Parsing Reward: Behavioral, neural, and pharmacological investigations of motivational and hedonic dimensions of reward

Dissertation
submitted to the
Faculty of Business, Economics and Informatics
of the University of Zurich

to obtain the degree of
Doktorin der Neuroökonomie, Dr. sc.
(corresponds to Doctor of Neuroeconomics, PhD)

presented by

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approved in October 2017 at the request of
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The Faculty of Business, Economics and Informatics of the University of Zurich hereby authorizes the printing of this dissertation, without indicating an opinion of the views expressed in the work.

Zurich, 25.10.2017

Chairman of the Doctoral Board: Prof. Dr. Todd Hare

Acknowledgments

To my advisor, Prof. Philippe Tobler: Thank you for all your support, both personal and academic. Thank you for your patient mentorship and guidance, and for introducing me to the rewarding wonder that is the brain.

To my mentor, Prof. Boris Quednow: Thank you for your supervision and for the many fruitful and interesting scientific discussions. I am truly happy to have had you on my team.

To my co-advisor, Prof. Todd Hare: Thank you for your time, your comments and helpful feedback.

To the SNS Lab, both past and present: You've been a constant source of support and fun, thanks for filling these last years with both interesting ideas and lots of laughter. I especially want to thank Silvia Maier for the many walks and talks that kept me sane throughout this process; Thorsten Kahnt for always having an open door and open ear to any questions or worries; and Karl Treiber for making the countless hours of scanning so enjoyable.

To my parents: Thank you for your constant encouragement, be it through making sure I had the time to write by watching Ravi, the energy to think by cooking food, or the peace of mind to work by simply listening to my gripes and doubts. Thank you for raising me to question assumptions and delve deeply into questions. Thank you for instilling in me a desire to read and study and learn.

To Gagan: Thank you for always being interested in my work, for challenging me and thereby making me think harder and probe further, for building me up when I had doubts, for always being there for me no matter what. I would not have been able to do this without you.

To Ravi: For making me smile after long days.

July 2017

Abstract

Reward is not a unitary construct but can be parsed into at least two dimensions: the motivational drive to seek out or work for rewards and the hedonic pleasure received from them. While animal studies suggest that these two dimensions can be dissociated and that they rely on separate neural and pharmacological systems, studies in humans have had mixed results. It is therefore unclear whether parsing reward into individual dimensions is helpful in informing our understanding of human reward processing. This thesis examines whether it is possible to dissociate the motivational *wanting* dimension and the hedonic *liking* dimension of reward behaviorally and neurally in healthy human volunteers. Moreover, it investigates how the prefrontal cortex (PFC) and striatum are involved in encoding these two dimensions, and how blocking the dopamine (DA) system influences reward encoding in general, as well as how blocking the DA and opioid system influences behaviors related to the motivational dimension of reward.

In the first study, participants were asked to perform wanting and liking judgments of everyday consumer items while undergoing functional imaging, before and after playing a simple perceptual game in which they won half of the items. The results indicate that participants could differentiate wanting and liking and that our task was able to dissociate these two dimensions behaviorally: (1) liking judgments took significantly more time than wanting judgments, and (2) liking decreased specifically for lost items, while wanting decreased specifically for won items. Furthermore, the two reward dimensions were encoded differently in the brain: anatomically distinct areas in the PFC encoded *either* wanting or liking regardless of judgment type, while common areas in the striatum encoded *both* wanting and liking depending on which judgment the participant was currently performing. Lastly, connectivity between the anatomically distinct wanting and liking areas and the striatum differed depending on which judgment the participant was making. Connectivity between the striatum and liking regions in the PFC was enhanced according to the level of liking during liking judgments. In contrast, connectivity between the striatum and wanting regions in the PFC was enhanced according to the level of wanting during wanting judgments. This suggests that cortico-striatal pathways may play an important gating function by

flexibly encoding the specific reward dimension that is currently behaviorally relevant.

The second study investigated neural encoding of reward in more detail, specifically focusing on how DA modulates reward encoding in the PFC. This was done by using a multivoxel pattern analysis technique to decode reward signals under DA blockade or placebo. Participants received either a D2-specific DA antagonist or a placebo pill approximately 1.5 hours before undergoing functional imaging of a non-instrumental outcome prediction task. D2-blockade led to enhanced encoding of reward related activity in the medial PFC: the decoding accuracy was significantly higher in subjects who had received the DA antagonist than in those that had received placebo. This suggests that blocking D2-DA receptors and biasing the system towards a D1 receptor dominated state enhances the stability of reward representations.

The third study investigated the role of DA and opioid receptor pharmacology in two behaviors related to the motivational dimension of reward: reward impulsivity and cue-induced responding. Participants received either a D2-specific DA antagonist, an unspecific opioid antagonist, or a placebo pill approximately three hours before completing a delay discounting task and a Pavlovian-instrumental transfer task. Both reward impulsivity, measured by the delay discounting task, as well as cue-induced responding, measured by the Pavlovian-instrumental transfer task, were reduced under DA and to a lesser extent under opioid blockade. These results are in line with animal studies demonstrating an effect of both dopamine and opioid modulation on the motivational dimension of reward.

Overall, our findings suggest that reward can be parsed into separate dimensions in humans and that these dimensions differ in how they are encoded in the brain. Furthermore, both reward encoding in the brain and reward-related behaviors are modulated by DA and to some extent opioid pharmacology. Parsing reward into separate dimensions may be useful when considering psychiatric disorders marked by aberrant reward processing, as it allows for a more precise characterization of the deficits and may lead to more specific treatment and therapy approaches.

List of manuscripts

The dissertation is based on the following research articles:

Study 1:

Weber SC, Kahnt T, Quednow BB, Tobler PN. Fronto-striatal pathways gate processing of behaviorally relevant reward dimensions. *In preparation.*

Study 2:

Kahnt T, Weber SC, Haker H, Robbins TW, Tobler PN (2015). Dopamine D2-Receptor Blockade Enhances Decoding of Prefrontal Signals in Humans. J Neurosci 35(9): 4104-4111.

Study 3:

Weber SC, Beck-Schimmer B, Kajdi M, Müller D, Tobler PN, Quednow BB (2016). Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced reward responding and reward impulsivity in healthy volunteers. Translational Psychiatry 6(7), e850.

Contents

1. Introduction

Reward is a fundamental driver of human behavior. Rewards motivate us to work, engage in relationships, procreate, eat, and learn, thereby shaping our everyday actions and plans. The subject of reward has been of interest to philosophers, religious thinkers, and scientists alike. Understanding how rewards influence behavior and how the human brain processes rewards has been debated since at least the first scientific definition of reward and its role in learning in Thorndike's *law of effect* (1911), where a reward is described as something that leads to a "satisfying state of affairs" and in turn strengthens the association or connection between a stimulus and an instrumental response that led to that reward. Since then, the definition of reward has evolved and changed numerous times. Recent models of reward suggest that it may be useful to parse reward into separate psychological dimensions to better understand how these dimensions can work together, in parallel, or even in opposing directions to drive human behavior. Two important dimensions that have been identified are the motivational drive to seek out rewards and the hedonic pleasure obtained from them. These dimensions are often correlated but can be dissociated by modulating dopamine (DA) and opioid levels.

Dopamine is a key neurotransmitter involved in reward processing. Many drugs of abuse, monetary gains, and even positive social interactions, activate the mesolimbic DA system. However, while it is clear that DA is important for reward processing and learning, its exact role is still debated. In this dissertation, I will present three studies (see Appendices) that investigate the neural as well as neurochemical underpinnings of reward, with emphasis on *whether* reward in humans can be decomposed into separate dimensions and *how* these dimensions are encoded in the brain. I will then discuss further which neurotransmitter systems are likely involved. In study 1, I tested whether reward can be dissociated behaviorally and neurally into hedonic and motivational dimensions, and furthermore, how the prefrontal cortex (PFC) and striatum encode these two dimensions. In study 2, I examined how reward information, in general, is encoded in the PFC and how this encoding is modulated by DA. Finally, in study 3, I explored the neurochemical underpinnings of reward in more detail, by investigating the role

of DA and opioid receptor pharmacology in reward impulsivity and cue-induced responding.

In the first introductory chapter, I will provide a brief overview of reward processing in humans, and touch upon aberrant reward processing in psychiatric disorders. I will describe the putative dimensions of reward, describe the neurobiology underlying reward, explain how the DA and opioid systems are hypothesized to be involved in reward processing, and lastly give an overview of the role of maladaptive reward processing in disease. The second chapter will summarize the three studies, which investigated reward using functional magnetic resonance imaging (fMRI; study 1), pharmacology and fMRI (study 2), and pharmacology and behavior (study 3). Finally, the third chapter will conclude with a general discussion of the results.

1.1 Parsing reward into separate dimensions

Many theories have attempted to explain what motivates individual behavior. One of the earliest, the *drive reduction theory*, suggests that behaviors result from a biological or physical imbalance in needs and the urge (drive) to regain a state of homeostasis (Hull, 1943; Mowrer, 1960; Spence, 1956). For example, when a person is hungry they will act in a way to reduce the discomfort of being hungry. However, while this theory can explain simple behaviors driven by intrinsic forces, it is not able to explain behaviors that arise when all biological needs are met, increased motivation in the presence of reward-predicting cues, or overconsumption of rewarding foods and liquids. Other theories that also rely on intrinsic internal drives, such as arousal theory (Hebb, 1955) or instinct theory (Freud, 1933), have similar shortcomings.

Early *incentive motivation theories* filled this void by proposing an alternative description of behavior, where behavior is motivated primarily by external rewards and outside incentives (Bindra, 1974; Bindra, 1978; Bolles, 1972; Toates, 1986). According to incentive motivation theories, stimuli can produce and shape behaviors if they have motivational or *incentive* properties. They obtain these properties by being paired with unconditioned rewards. This happens often in everyday life, for example when the smell of food is consistently paired with its

consumption, after a while the smell alone may produce or increase hunger and consequently food seeking behavior. Notably, a key idea of these theories is that the amount of effort exerted or the amount of motivation exhibited to obtain a reward is directly proportional to the amount of pleasure the individual receives from the reward. According to these theories, a hungry individual will act to reduce hunger and will do so with more vigor and/or speed in the presence of cues (such as odor or visual stimuli) that were previously paired with pleasantly tasting food. For a long time, this view of reward dominated, with reward considered a unitary construct, in which different dimensions of reward – such as the drive to seek out rewards and the pleasure received from them – were so thoroughly integrated that they were used interchangeably.

However, this unitary, hedonic view of reward under incentive motivation theories was challenged later on. For example, Berridge, Robinson, and colleagues performed a series of rodent experiments, which indicated that the motivational and hedonic dimensions of rewards are not always aligned (Berridge and Robinson, 1998; Robinson and Berridge, 1993). They could show that blocking the mesolimbic DA system through lesions resulted in a stark reduction of instrumental (motivated) behavior while leaving hedonic pleasure reactions largely unaffected (Berridge and Robinson, 1998). Similarly, increasing the level of DA increased the drive of the animal to seek out rewards (instrumental behavior), while leading to no comparable increase in hedonic responding (Wyvell and Berridge, 2000). In contrast, modulating the endogenous opioid system, specifically in small hot spots in the nucleus accumbens (NAc) and the pallidum, modified hedonic pleasure reactions (Castro and Berridge, 2014; Mahler et al., 2007; Smith and Berridge, 2007). In sum, the *incentive salience theory* proposed by Berridge and colleagues parses reward into at least two dimensions, the motivational *wanting* dimension of reward that drives instrumental behavior and is largely dependent on the mesolimbic DA system, and the hedonic *liking* dimension of reward that is related to the pleasure received from the reward and is largely dependent on the endogenous opioid system. These two dimensions differ in their anatomy and pharmacology, and can under certain circumstances be driven in opposing directions (i.e. when a reward is wanted but not liked or vice versa).

While the incentive salience theory has been tested and supported in numerous animal experiments, in humans the picture is less clear. Some evidence in favor of it comes from patients with clinical disorders marked by a deregulation of the DA system. In these patients, wanting of rewards is at times disconnected from liking of rewards. For example, Sherdell and colleagues (2012) considered the role of wanting and liking in mitigating depression. They asked both healthy controls and currently depressed participants to rate how much they liked a series of cartoons and assessed wanting by measuring the amount of effort they were willing to exert to view a cartoon. As expected, in the control group liking of the cartoon was strongly correlated with the amount of effort that the participant was willing to exert. In contrast, for the depressed group, liking did not predict subsequent effort levels. In line with this, Ostafin and colleagues (2010) found that in at-risk alcohol drinkers, those that had a long history of drinking exhibited a dissociation between liking ratings of an alcoholic drink and the amount they subsequently consumed. The correlation between the two measures was decreased compared to participants with a shorter history of drinking. These dissociations between wanting and liking in clinical disorders support the idea of separate reward dimensions in humans.

However, other studies have provided conflicting evidence for parsing reward into motivational and hedonic dimensions. Some studies have offered supporting results: Similar to animal studies, stress induction can increase cue-triggered wanting of an olfactory reward in healthy human participants, without a similar increase in pleasure ratings (Pool et al., 2015). Furthermore, DA levels in the ventral striatum (VS) are more strongly correlated with subjective "wanting" ratings of a reward than with subjective pleasure or "liking" ratings of the same reward (Leyton, 2002; Evans et al., 2006). Similarly, reducing DA levels reduces cue- and cocaine-induced cravings related to wanting without decreasing the reinforcing euphoria more closely related to liking (Leyton et al., 2005), in line with the notion that the DA system is preferentially involved in reward-related motivation rather than hedonics. However, contradictory findings also exist: Barrett and colleagues (2004) report a correlation between DA levels and the pleasurable, euphoric drug effects in smokers, and not with self-reported craving. Tibboel and colleagues (2011) failed to find any dissociation between wanting and liking using implicit measures. This has led some researchers to strongly challenge the idea of separate

motivational and hedonic reward dimensions, especially for food rewards (Havermans, 2011, 2012).

Conflicting results of studies investigating different reward dimensions in humans may due to several methodological reasons. One shortcoming of many of these studies is their operationalization of wanting and liking (Pool et al., 2016). Many studies do not use the same measure for determining wanting and liking, making it difficult to form direct comparisons. Any differences in wanting and liking reported by those studies could, therefore, be due to differences in the measurement instrument, instead of the reward dimension. Secondly, the common use of food rewards may be problematic, as wanting and liking of foods is so intrinsically connected that it could be difficult for study participants to dissociate these two constructs (Havermans, 2011, 2012). Lastly, studies using drug rewards and measuring craving as well as euphoric drug effects have very low sample sizes, often with less than 10 subjects. It is therefore still a matter of debate whether human reward can be decomposed into specific dimensions and if these dimensions differ in their neural anatomy and pharmacology.

1.2 Neural processing of reward

As reward processing is made up of several complex sub-processes – including anticipation, planning to attain, experiencing, as well as updating the relative value of a reward – a myriad of brain regions is recruited and involved. For this thesis, I will focus specifically on reward encoding and restrict myself to investigating the primary anatomical target regions of DA: the striatum and the PFC.

In the past decades, considerable interest has focused on how rewards are encoded in the human brain. One consistent finding is that a multitude of different rewards – from primary rewards, such as foods and drugs, to secondary rewards, such as money or consumer goods – activate a shared network of brain regions, especially the PFC and striatum (Bartra et al., 2013; Peters and Buechel, 2010). A key question is how these different types of rewards and complex situations are represented in the brain to compute value signals that inform choices. For example, how does the brain encode and compare the choice between eating a delicious cookie and going jogging – two very different reward categories? How can the same

reward, such as a chocolate bar, have different value representations depending on whether someone is hungry or satiated? How are different aspects of a reward encoded in the brain of an addict who has a strong craving and desire for a drug, even though this drug will not provide him with high levels of pleasure? All these questions illustrate the complexities involved in reward encoding, which needs to account both for features of the reward (such as size, pleasantness, attractiveness, and health benefit) and the current state of the individual (such as metabolic and physiological variables, and mood).

A key brain region involved in reward encoding is the ventromedial prefrontal cortex (vmPFC). The vmPFC is typically active during decision making tasks and signals in the vmPFC scale with the value of the presented items or outcomes, with increasing value increasing vmPFC activity and decreasing value decreasing vmPFC activity (Plassmann et al., 2010; Tom et al., 2007). Notably, the vmPFC encodes rewards in an abstract, general manner, allowing for comparisons of rewards of different reward categories. For example, the subjective value of food items, consumer items, as well as monetary rewards are all encoded in an overlapping region in the vmPFC (Chib et al., 2009). An adjacent region to the one reported by Chib and colleagues also encodes both the subjective value of charitable donations (Hare et al., 2010), as well as food rewards (Hare et al., 2008; Plassmann et al., 2007). Studies using multivariate pattern classifiers on fMRI signals of different reward categories have recently substantiated these findings. Using signals from the vmPFC, classifiers trained on the value of food rewards are able to decode the value of non-food consumer goods (McNamee et al., 2013), and neural patterns in the vmPFC related to reward information of faces correlate with neural patterns in the vmPFC related to reward information of places (Pegors et al., 2015). Signals in the vmPFC have not only been shown to be category-independent but also identity-independent: classifiers trained on the value of a specific savory food odor are able to decode the value of a specific sweet food odor (Howard et al., 2015; Howard and Kahnt, 2017). Notably, this general encoding of rewards in the vmPFC occurs even in the absence of decision-making tasks, when only incentive cues of different reward categories are presented (Kim et al., 2011). Identity- and category-general (or common currency) encoding of reward signals has been replicated consistently in numerous studies (Chib et al., 2009; Howard et al., 2015; Kim et al.,

2011; Lebreton et al., 2009; Levy and Glimcher, 2011; Lin et al., 2012; McNamee et al., 2013; Plassmann et al., 2007; Smith et al., 2010, see also the meta-analysis by Levy and Glimcher, 2012). It seems that the vmPFC may, therefore, be important in encoding reward for comparisons across reward categories.

A second important region for neural reward encoding is the orbitofrontal cortex (OFC), which is often implicated in tasks involving goal-directed behavior and reward processing. The OFC can be functionally divided into lateral, central and medial OFC (Kahnt et al., 2012). Just like in the vmPFC, signals in the medial OFC have been shown to be category- and identity-independent, and different rewards are encoded on a similar scale (Chikazoe et al., 2014; Klein-Flügge et al., 2013, see also the meta-analysis by Levy and Glimcher, 2012). This is not surprising, given the overlap of vmPFC and medial OFC. However, in contrast to the general reward encoding in the medial OFC, signals in the lateral OFC are identity-specific (Howard et al., 2015; Boorman et al., 2016; Howard and Kahnt, 2017; Klein-Flügge et al., 2013; Sescousse et al., 2010). In other words, different rewards are encoded differently in the lateral OFC even if they are valued the same. For example, the same level of subjective value of a certain sweet and a certain savory odor are encoded in unique patterns in the lateral OFC. A pattern classifier trained on value signals of one rewarding odor is not able to accurately decode the value of a different but equally rewarding odor type (Howard et al., 2015). Another key aspect of reward encoding in the lateral OFC is that signals are modulated by the current physiological state of the individual. This can be investigated using devaluation paradigms, in which participants are sated on a specific appetitive reward to reduce its subjective value. Both animal (Gallagher et al., 1999; Murray et al., 2015; Rhodes and Murray, 2013; Rudebeck et al., 2013) and human studies (Gottfried et al., 2003; Howard and Kahnt, 2017) have shown that the OFC is involved in devaluation: Animals with OFC lesions continue to seek out devalued rewards. In humans, devaluation changes the identity-specific reward signals of a sated odor in the lateral OFC. In sum, the OFC encodes reward both in an identity-specific, as well as common-scale manner, including information about the organism's current state.

Besides the vmPFC and OFC, the striatum is another region that is vital for reward encoding. As with the vmPFC, reward encoding in the striatum is thought to occur in a more general manner. Activity in the striatum scales with reward value

for both gains and losses (Tom et al., 2007), as well as for different reward categories (Levy and Glimcher, 2012). Sescousse and colleagues (2010) had male participants experience either monetary or erotic rewards. Their results indicated that in contrast to reward-specific signals in the lateral OFC, the striatum commonly encoded both monetary and erotic rewards, suggesting a more general processing of reward in this region. Similar results of common value signals in the striatum have been found for monetary and social rewards (Izuma et al., 2008, 2010), as well as monetary and juice rewards (Valentin and O'Doherty, 2009). Furthermore, activity in the striatum scales with the subjective value of both social and monetary reward-predicting cues (Rademacher et al., 2010; Spreckelmeyer et al., 2009), as well as for both erotic and monetary reward-predicting cues (Sescousse et al., 2015), even in the absence of decision making.

Taken together, through both general reward signals and identity-specific reward signals in the PFC and striatum, the brain can encode and compare rewards from multiple categories on a common scale while maintaining important reward specific information. Critically, it seems that neural signals encode both value information, as well identity information about rewards. One subsequent question is therefore: is reward dimension-specific information also encoded in the PFC or striatum?

As reward can be parsed into individual psychological dimensions – the motivational dimension and the hedonic dimension – it seems probable that these two dimensions are also encoded in the PFC and/or the striatum. While the OFC has been proposed as a key component of the pleasure network in the human brain (Berridge and Kringelbach, 2015), the striatum has been implicated in processing appetitive, motivational value signals in both human and non-human animals. In rodents, studies have demonstrated increases in instrumental responding for rewards after DA modulation in the VS (Wyvell and Berridge, 2000). Furthermore, McGinty and colleagues (2013) recorded cue-evoked neuronal firing to reward-predicting cues in the VS and found that the recorded signals were directly related to the reward-seeking behavior as well as the vigor and speed of subsequent instrumental responding. In humans, Schmidt and colleagues (Schmidt et al., 2012) found that activity in the striatum was related to how much cognitive or physical effort participants exerted in order to receive a reward. In line with this, Sescousse

and colleagues (2015) showed that response times to reward-predicting cues were negatively correlated to the striatal activity elicited by these cues. Together, the emerging framework relates the OFC more closely to pleasure and the hedonic dimension of reward, whereas the striatum appears more involved in processing incentive value that drives behavior, so more closely related to the motivational dimension of reward.

However, this straightforward picture of prefrontal processing of hedonic reward dimensions and striatal processing of motivational reward dimensions is complicated by several studies reporting activity related to pleasure in the striatum (Blood and Zatorre, 2001; Rolls et al., 2008), as well as those reporting activity related to incentive motivation in the medial prefrontal cortex (mPFC), including the OFC and vmPFC (Arana et al., 2003; Kringelbach, 2005). These seemingly contradictory findings may not be surprising, given that the hedonic and motivational dimensions of reward are typically aligned and most studies do not control for the other dimension.

In their review in 2010, Peters and Buechel highlight the diversity of findings related to neural reward processing, and thereby also provide evidence of limitations in dissociating wanting from liking. Peters and Buechel report that both activity related to liking, which they refer to as outcome value, as well as activity related to wanting, which they refer to as goal value and decision value, have been found in the OFC and vmPFC. Activity in the striatum has been related to both outcome values and decision values. However, the variability in methodology among the reviewed papers introduces issues of interpretability regarding findings of wanting and liking in humans. The studies differed vastly in both the reward types that were used, as well as in the measure of value that was employed. While liking (outcome value) studies typically used sensory rewards, such as music, olfactory, or gustatory rewards that were experienced immediately, wanting (goal/decision value) studies typically used either food or monetary rewards which were delivered post task. Secondly, while liking studies used ratings to measure the hedonic value, wanting studies mostly used a Becker-DeGroot-Marschak (BDM) auction or choice tasks to measure goal or decision value. These systematic differences in reward type (sensory primary rewards vs secondary rewards), in reward timing (immediate consumption vs post task delivery), as well as in reward measure (ratings vs

BDM/choice tasks), make comparisons between wanting and liking nearly impossible. This is further complicated by the fact that, as mentioned previously, past studies generally investigated only one dimension without controlling for the other.

1.3 The dopamine system and reward

DA plays an important role in the reward system. Midbrain DA neurons are associated with reward prediction, reward prediction error, reward anticipation, as well as reward receipt. Increases in DA release have been observed for pleasant music (Salimpoor et al., 2011), monetary (Koepp et al., 1998; Zald et al., 2004), and drug rewards (Brody et al., 2004; Drevets et al., 2001; Volkow et al., 1996), as well as for cues associated with these rewards (Volkow et al., 2006). The majority of DA cell bodies locates in the ventral midbrain (particularly the ventral tegmental area (VTA) and substantia nigra), from where the axons diverge to several terminal areas in the forebrain and cortex. Thereby, DA can modulate the cortico-striatal loops as part of the basal ganglia circuit (Graybiel and Grafton, 2015; Haber, 2014). Together, the mesolimbic and nigrostriatal DA system as well as limbic and cortical areas, including the VS, dorsal striatum, OFC, and anterior cingulate cortex (ACC), form a *reward circuit* (Goldstein and Volkow, 2002; Haber and Knutson, 2010).

Extracellular DA acts by binding to pre- and postsynaptic DA receptors. DA receptors are most abundantly found in the striatum (Dawson et al., 1986), but also occur in the PFC (Durstewitz and Seamans, 2008; Lidow et al., 1989; Seamans and Robbins, 2010). Broadly speaking, there are two types or families of DA receptors: D1 and D2. These two receptor types differ in two key properties: (1) While D1-DA receptors function in an excitatory manner, increasing the likelihood of neuronal firing, D2-DA receptors function in an inhibitory manner, reducing the likelihood of neuronal firing (Surmeier et al., 2007); and (2) while D1-DA receptors are more sensitive to phasic changes in DA levels, i.e. to shorter burst activity, D2-DA receptors are more sensitive to tonic DA levels, i.e. to continuous activity (Dreyer et al., 2010).

One prominent theory of prefrontal DA functioning, the *dual-state theory*, harnesses the different properties of D1 and D2 receptors. According to this theory,

the type of DA receptors that are preferentially activated may play an important role in neural processing (Durstewitz and Seamans, 2008): When neural networks are in a D1-dominated state, cognitive representations are more stable, whereas neural networks in a D2-dominated state are more flexible. This is in line with studies indicating that D2-DA receptor function plays a critical role in tasks that require flexible behaviors, such as attentional set shifting and response flexibility, in both animals (Floresco et al., 2006; Goto and Grace, 2005) and humans (Mehta et al., 2004; Tost et al., 2006, but see also Luciana and Collins, 1997; Mehta et al., 2001 for conflicting results). D1 receptors, on the other hand, are critical for successful performance in working memory tasks (Abi-Dargham et al., 2002; Constantinidis and Klingberg, 2016; Sawaguchi and Goldman-Rakic, 1991). However, the exact function of the D1- and D2-DA receptors, especially with respect to reward processing, has remained elusive.

In contrast to dual-state theory, incentive salience theory (like other frameworks) takes a more holistic perspective on DA functioning. It emphasizes DA as an integral part of the motivational dimension of reward. In this view, motivational salience of stimuli and consequent increases in motivation intensity brought about by reward cues, are generated by the mesolimbic DA system and the mesocorticolimbic reward circuit. As discussed in section 1.1, numerous animal experiments have provided evidence of modulations of the incentive salience of rewards and subsequent modulations in reward-seeking behaviors following both tonic and phasic DA level fluctuations. However, it is important to note that there are also prominent alternative interpretations of the role of DA in reward processing, which emphasize the role of DA in subjective value processing, in reward prediction error processing and reward learning (Salamone and Correa, 2002; Schultz, 1998; Wise, 1982).

1.4 The opioid system and reward

Less is known about the exact role of the opioid system in reward. In general, the opioid system comprises three types of receptors: mu, delta, and kappa opioid receptors. These receptors are activated by endogenous opioid peptides in response to rewarding stimuli (van Ree et al., 2000). Opioid receptors are distributed

throughout the brain, with highest concentrations in the cortex, limbic system and brainstem (LaMotte et al., 1978; Le Merrer et al., 2009; Mansour et al., 1987; Mansour et al., 1988).

Functionally, the opioid system has been linked to reward and reinforcement more generally. Endogenous opioid release in the VS has been observed following painful as well as pleasant events (Szechtman et al., 1981; Zubieta et al., 2001). In animals, opioid receptor activation in spatially restricted hotspots within the pallidum and NAc leads to increased pleasure reactions (Smith and Berridge, 2007). In line with this finding, in humans opioid antagonism leads to a reduction in pleasantness ratings of sweet solutions (Arbisi et al., 1999; Fantino et al., 1986), as well as a reduction in hedonic responses to food items (Drewnowski et al., 1995; Yeomans and Gray, 1996, 1997). The opioid system is also involved in the reinforcing effects of drugs of abuse (Contet et al., 2004; Kieffer and Gavériaux-Ruff, 2002; Le Merrer et al., 2009; Nutt, 1999). However, whether opioid agonists and antagonists influence reward processing directly through the opioid system or indirectly through opioid-DA interactions is still a matter of debate. On the one hand, studies using DA-depleted mice indicate that in opioid-naïve animals activating midbrain mu opioid receptors can produce reward signals and lead to learning, suggesting that DA is not necessary for this (Hnasko et al., 2005). On the other hand, the DA and opioid system are closely connected anatomically (Khachaturian and Watson, 1982). Pharmacologically, opioid antagonists can block DA release induced by alcohol or feeding (Benjamin et al., 1993; Taber et al., 1998), and opiates are able to indirectly disinhibit and excite DA neurons (Chartoff and Connery, 2014; Johnson and North, 1992; Luscher and Malenka, 2011; Nutt, 1999). In turn, DA modulation influences opioid levels, with phasic DA leading to increases in opioid levels (Roth-Deri et al., 2003). Lastly, in humans who have a genotype that affects dopaminergic neurotransmission, the response of the opioid system is also altered. Zubieta and colleagues (2003) found higher regional density of mu-opioid receptors in participants with enhanced activity of the dopaminergic system due to a genetic variation in the catechol-O-methyltransferase gene. Taken together it is, therefore, possible that the rewarding effects of opioids are generated by interactions between the DA and opioid system, instead of the opioid system alone.

1.5 Aberrant reward processing

Maladaptive reward processing is associated with numerous psychiatric disorders, including substance use disorders, depression, eating disorders, behavioral addictions, affective disorders, and schizophrenia (Arias-Carrion et al., 2010; Davis et al., 2009; Grace, 2016; Romer Thomsen et al., 2014; Zald and Treadway, 2017). Deficits can present as reduced reward sensitivity, apathy or anhedonia, or as increased reward responding, excessive goal-related activity or increased reward impulsivity. These types of deficits can be observed in tasks related to reward processing, such as those measuring responding to reward-related cues or requiring inhibition of impulses to attain higher rewards.

Patients suffering from disorders marked by maladaptive reward processing typically also suffer from deregulation of the DA or opioid system. Such deregulation can be aptly illustrated using the example of drug addiction. Patients suffering from substance abuse often exhibit neural changes in the mesolimbic DA and opioid system. Prolonged drug use can cause both sensitization of the DA system by increasing DA release, as well as tolerance by decreasing the sensitivity of DA receptors and by reducing the expression of DA receptors (Berke and Hyman, 2000; Volkow et al., 2009). Notably, while tolerance mechanisms are usually able to recover quickly, neural sensitization is much more permanent and can continue for years (Dalia et al., 1998; Kalivas and Duffy, 1993; Paulson et al., 1991). At the neural level, *incentive* sensitization, i.e., greater DA reactivity to drugs as well as cues associated with drug use, is considered a strong factor in inducing cravings and contributing to relapse (Robinson and Berridge, 1993; Robinson and Berridge, 2001, 2008). Prolonged drug use also modifies endogenous opioids and opioid receptors (Waldhoer et al., 2004). However, how exactly changes in the opioid system contribute to drug craving and relapse is still unclear.

Linking difficulties in reward processing to changes in the DA or opioid system is of great interest to those trying to understand how addiction develops as well as why there is such a high incidence of relapse. Understanding how DA and opioid pharmacology influences tasks involving reward processing may help illuminate how these neurotransmitter systems are involved in diseases marked by aberrant reward processing, and in turn, these insights may allow for the development of potentially new and more specific treatments. Furthermore, they

may help fine-tune psychotherapy techniques which aim at improving reward-related deficits, such as behavioral activation therapy, future-directed therapy, and motivational interviewing (Zald and Treadway, 2017).

Aberrant and healthy motivational effects of reward-associated stimuli can be measured with **cue-induced responding.** Cue-induced responding refers to the ability of a previously learned Pavlovian cue to elicit instrumental behavior even in the absence of reward and even when the Pavlovian cue was never paired with the instrumental response directly. The idea is that the Pavlovian cue has acquired incentive salience and this allows it to induce and increase instrumental responding. Cue-induced responding is used as a model for drug craving mechanisms underlying relapse and may also be applicable to overeating or other forms of excessive reward seeking (Johnson, 2013; Lamb et al., 2016; Smith and Robbins, 2013).

Cue-induced responding is typically measured by Pavlovian-instrumental transfer (PIT) tasks. These tasks have a three-stage design consisting of a Pavlovian conditioning phase, an instrumental conditioning phase, and a transfer test. In an initial Pavlovian conditioning phase, a specific Pavlovian cue is paired with a reward. After successful Pavlovian conditioning, the instrumental conditioning phase begins. Here a particular instrumental response increases the probability of a reward and the participant learns this association. Lastly, a transfer test takes place under extinction conditions, i.e. without the presentation of any rewards. Here, instrumental responding is measured both in the absence and in the presence of the Pavlovian cue. In animal models, as well as healthy human volunteers, the Pavlovian cue will reinstate or increase instrumental responding in the transfer test phase relative to baseline (Lamb et al., 2016).

Patients suffering from psychiatric disorders linked to deficits in reward processing often exhibit altered cue reactivity. Drug-dependent, overweight and obese individuals have stronger neural signals in response to drug or food related cues respectively (Smith and Robbins, 2013). Furthermore, increased cue reactivity in patients suffering from substance abuse, especially increased neural reactivity to drug cues, is associated with an increased relapse risk and resistance to treatment (Courtney et al., 2016). In contrast, cue reactivity is reduced in subjects undergoing treatment as opposed to those actively using drugs, especially in those reporting a high motivation to reduce their drug use (Prisciandaro et al., 2014; Wilson et al.,

2004). Pharmacologically, cue-induced responding has been linked to both the DA (Dickinson et al., 2000; Ostlund and Maidment, 2012; Peciña et al., 2006; Wassum et al., 2011; Wyvell and Berridge, 2000) and the opioid system (Laurent et al., 2012; Peciña and Berridge, 2013) in several animal studies, but it remains unclear if this is also the case in humans.

An alternative measure for motivational reward functions is **reward impulsivity.** Reward impulsivity is defined as the inability to delay gratification and wait for a larger reward in the face of a smaller immediate reward (Dalley and Robbins, 2017). Increased reward impulsivity may be a reason why drug use is started and maintained (Wit, 2009), as the immediate reward of the drug is valued more than distant long-term rewards, such as intact relationships, stable income, or good health. This form of impulsivity may also play a role in explaining other disorders marked by maladaptive reward processing, such as eating or gambling disorders.

Reward impulsivity is often measured by delay discounting (DD) tasks, in which participants are asked to make a series of choices between larger, later rewards and smaller, immediate rewards. The ability to wait for larger later rewards has been linked to a number of positive life outcomes and beneficial life skills, including academic and financial success, good health, better ability to deal with stress and adversity, and higher self-esteem. In turn, increased reward impulsivity is associated with an increased risk for substance use disorders and higher rates of obesity (Mischel et al., 2011; Moffitt et al., 2011).

Like in cue-induced responding, patients with substance use disorders often display elevated reward impulsivity (Bickel et al., 2011; Coffey et al., 2003; Havranek et al., 2017; Hulka et al., 2014). Furthermore, increased reward impulsivity is related to higher drug consumption and lower treatment success (Brody et al., 2014; Washio et al., 2011). However, it is unclear whether this is caused by the drug use per se or if this is a personality trait that predisposes one to substance use. Pharmacological studies of reward impulsivity have shown an involvement of both the DA (Floresco et al., 2008; Pine et al., 2010, 2010; Wit et al., 2002) and opioid system (Kieres et al., 2004; Love et al., 2009; Pattij et al., 2009) in reward impulsivity.

2. Overview of the studies

Understanding how reward is processed in the brain, as well as what neurotransmitters are involved, is crucial for elucidating normal as well as maladaptive decision-making. As we have seen, evidence primarily from past animal research, but also from human research, suggests that reward can be parsed into at least two dimensions: a motivational dimension and a hedonic dimension. Furthermore, it seems that these different reward dimensions also differ in their neurochemical underpinnings, with DA playing an important role in the motivational dimension of reward while leaving the hedonic dimension of reward largely unaffected. While the hedonic dimension is not influenced by modulations of the DA system, it does respond to changes in the endogenous opioid system. We, therefore, used both functional imaging as well as pharmacological approaches to investigate the two reward dimensions in more detail and test the role of the two different neurotransmitter systems involved.

In study 1, we conducted an fMRI experiment to test whether human reward processing can be dissociated behaviorally and neurally into motivational and hedonic dimensions. Additionally, we investigated how reward signals are encoded in the PFC and striatum and how reward information may be transferred from the cortex to the striatum in cortico-striatal loops. After establishing that both motivational and hedonic dimensions of reward are encoded in the PFC, we investigated these reward signals in more detail in study 2. Here we manipulated DA pharmacologically, to understand how DA antagonism affects reward encoding in the PFC. Lastly, in study 3, we studied the motivational aspect of two reward-related behaviors outside of the scanner – cue-induced responding and reward impulsivity – after applying DA or opioid pharmacology.

2.1 Study 1: Fronto-striatal pathways gate processing of behaviorally relevant reward dimensions

Background

To direct behaviors appropriately and make rational decisions, it is important to accurately evaluate rewards obtained from those decisions. The VS and PFC are two key areas involved in reward processing of primary, secondary, as well as social rewards (Bartra et al., 2013). The VS both receives input from the mPFC and the OFC, and indirectly projects to the OFC and ACC via the pallidum, the substantia nigra, and the thalamus (Haber, 2014). However, while the involvement of the VS in reward processing is clear, it is still uncertain how it encodes reward and how it channels behaviorally relevant reward information.

To probe whether the VS encodes only behaviorally relevant reward information, we used a task that separates reward into motivational wanting and hedonic liking dimensions. As described in detail in section 1.1, animal studies have consistently shown that these two dimensions can be differentiated neurally, with wanting relying mainly on the mesolimbic DA system and liking relying on the endogenous opioid system. Importantly, both wanting and liking engage spatially overlapping parts within the VS. If the VS acts as a gatekeeper, encoding the behaviorally relevant information, then reward-related activity in the VS should reflect the specific reward dimension that is important to direct behavior at that time. In this case, activity in VS should be associated with wanting during wanting judgments and with liking during liking judgments. In contrast, if the VS processes reward in a parallel manner, both wanting and liking dimensions should be engaged during wanting and liking judgments, with the two dimensions activating dissociable areas within the VS.

Methods

We asked twenty-eight right-handed participants (14 females) to rate forty everyday items in the fMRI scanner according to how much they wanted and liked them. Participants first saw a cue indicating the type of rating trial (1s), followed by an image of an item (3s), and finally the rating screen (3.5s) (Appendix 1, Figure 1). Ratings were provided on a continuous scale using a trackball. Trials were separated

by a variable inter-trial-interval (mean 3s). Each item was rated twice for wanting and twice for liking, resulting in 160 trials split into 4 runs. The ratings in the scanner were collected twice – once before and once after the participants played a perceptual game in which they won half of the items (each item was randomly assigned to win or lose). The game allowed us to separate wanting and liking more strongly, while also making the task more engaging.

Preprocessing and analysis of the fMRI data was done with the statistical parametric mapping software suite (SPM8). The raw fMRI time series were realigned, coregistered, segmented, normalized, and smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 4 mm. To extract wanting and liking related neural activity, we used two parametric general linear models (GLMs). The first model pooled data from both wanting and liking trials and included one onset regressor for every trial with three parametric modulators, the mean (over the two repetitions of the same object) wanting rating, the mean liking rating, and the response time. The second model separated wanting and liking judgments and consisted of one onset regressor for the wanting judgments and one onset regressor for the liking judgments. Both onset regressors were modulated by the same three parametric modulators as in the first GLM (mean wanting rating of the item, mean liking rating of the item, and response time). Head movements were included as nuisance regressors in both parametric GLMs. We performed a whole brain parametric analysis, as well as a region of interest (ROI) and psychophysiological interactions (PPI) analysis.

Results and conclusions

We found that after winning and losing the items, wanting and liking ratings changed in opposite directions. While wanting decreased specifically for won items and remained constant for lost items, the opposite was true for the liking ratings, which decreased specifically for lost items and remained unchanged for won items. Interestingly, the response times for the two judgment types also differed, with liking judgments taking significantly longer than wanting judgments. Together, this indicates that our subjects differentiated between the two judgment types.

Wanting and liking differed on the neural level as well. We found that wanting ratings were related to frontal activity, including parts of the medial OFC

and ACC/mPFC, as well as VS. In contrast, liking-related activity was more focal and limited to the central OFC, posterior cingulate, pallidum, and VS. This is in line with past rodent studies linking the VS to wanting and liking, and implicating the pallidum primarily in liking (Smith and Berridge, 2007; Wyvell and Berridge, 2000). Furthermore, we found that while the wanting and liking-related signals in the VS were overlapping and common to both reward dimensions, those in the OFC and mPFC were spatially segregated and specific to either wanting or liking.

We were particularly interested in how the striatum and PFC encode behaviorally relevant reward. Specifically, we asked whether these regions switch between the wanting and liking dimensions of reward according to the dimension being expressed in the current judgment. For the OFC, wanting and liking related reward signals were present regardless of judgment type. The wanting ROIs in the medial OFC encoded wanting ratings during both wanting and liking judgments. Similarly, the liking ROIs in the central OFC encoded liking ratings regardless of judgment type. In contrast, activity in the VS expressed one or the other rating as a function of the judgment type that the participant had to perform. Thus, signals in the VS reflected the liking ratings during liking judgments and the wanting ratings during wanting judgments. These data indicate that unlike prefrontal reward encoding regions, striatal value encoding regions flexibly switch to encode the reward dimension that is currently behaviorally relevant.

We next asked whether the differential encoding pattern in the VS and PFC would also translate into differential connectivity between the VS and the prefrontal liking and wanting ROIs depending on the type of judgment that the participant was making. Using a PPI analysis, we found that in fact, during liking judgments, the connectivity between the VS and the liking ROI in the OFC was stronger for the liking rating than the wanting rating. This was reversed for the wanting judgments, where the connectivity between the VS and the wanting ROI in the mPFC was stronger for the wanting rating than the liking rating.

In sum, we demonstrated that the PFC processes reward in a more automatic, parallel manner, while the VS acts as a gate, processing what is currently relevant for behavior. By using a task that asked participants to rate well-established dimensions of reward, we could show that while the PFC encodes wanting and liking dimensions in a spatially dissociated fashion, irrespective of judgment type, one and

the same VS region encodes only what is currently behaviorally relevant to the participant. This value selection function is implemented by a stronger connectivity for the liking ratings than the wanting ratings between the VS and the liking regions in the central OFC during liking judgments, as well as stronger connectivity for the wanting ratings than the liking ratings between the VS and the wanting regions in the mPFC during wanting judgments.

2.2 Study 2: Dopamine D2-Receptor Blockade Enhances Decoding of Prefrontal Signals in Humans

Background

The PFC plays an important role in goal-directed behavior, learning and decision making. To accomplish this role, it is vital for reward-related information to be represented and maintained in the PFC for later use. However, it is still largely unclear how the PFC implements such a representation. Past studies suggest that DA may play a key role in modulating prefrontal representations (Cools, 2011), and the dual-state theory offers a physiologically plausible computational model that describes the effects of DA on the PFC neurons in a receptor-specific manner: In the D2-dominated state, network representations are weaker than in the more stable D1-dominated state, making them more prone to interference and disruption, but also allowing for greater flexibility, as several weak network representations can exist simultaneously (Durstewitz and Seamans, 2008; Seamans and Robbins, 2010). In line with this theory, D2 receptor blockade – favoring a D1-dominated state – should enhance PFC representations of reward, by inhibiting concurrent representations of distractors. This, in turn, should result in more stable and enhanced network representations.

In this study, we used a D2-specific DA antagonist to probe whether D2 receptor blockade results in enhanced network representations of rewards in humans. We used a multivoxel pattern analysis (MVPA) technique to decode reward signals from the PFC. We hypothesized that blocking D2 receptors would lead to enhanced network representations which would allow for enhanced decoding of neural reward patterns through MVPA, i.e. greater decoding accuracy.

Methods

We conducted a between subject, randomized, double-blind, placebo-controlled fMRI study to investigate whether D2-DA receptor blockade enhances decoding of reward signals in the OFC. Fifty-one male subjects (placebo group n=24, amisulpride group n=27) performed a non-instrumental outcome prediction task approximately 1h 30min after receiving either a placebo pill or 400mg amisulpride. Amisulpride is a selective D2/D3-DA receptor antagonist and the dosage used in this study usually results in ~50–80% D2 receptor occupancy. To enhance and equate absorption of the drug across participants, all participants were instructed not to eat for at least 6 h before arriving on the day of the study. During the task, participants saw four visual cues, two of which were always associated with reward (0.20 Swiss Franc (CHF)) and two of which were never associated with reward (0.00 CHF). The visual cues were counterbalanced across subjects and the outcomes were presented either as images of coins or as numerical digits, in order to avoid interference from visual features of the cue-outcome pairs. This resulted in two stimulus sets (I and II), each consisting of a visual cue predicting reward and a visual cue predicting no reward and either the resulting coin or numerical outcome image.

Before scanning, subjects completed one training session in order to learn the cue-outcome associations. After the training session, participants were placed in the fMRI scanner and the non-instrumental outcome prediction task started. This task comprised five runs, with 10 presentations of each cue-outcome pair. For each presentation, the visual cue was displayed for 0.6s, after which participants had 1.5s to indicate what they anticipated the upcoming outcome (reward or no reward) to be, followed by the outcome (1s), and a variable inter-trial interval with a mean of 3.5s.

We used linear support vector classification (SVC) combined with a searchlight approach, to decode reward representations, i.e. representations associated specifically with reward as opposed to no reward. This MVPA technique can detect response patterns that are condition specific and can be classified as reward trials or no reward trials through pattern recognition algorithms.

Using unsmoothed data, we first estimated a GLM containing four regressors for the onset of each of the four cue-outcome pairs, as well as six head movement regressors of no interest. The parameter estimates of the four regressors of interest,

corresponding to the response amplitude to each of the four cue-outcome pairs, were then used as inputs to a subject-wise linear SVC analysis combined with a searchlight-decoding approach (searchlight sphere 10mm radius). In an initial step, using only stimulus set I, the SVC model was trained to classify patterns of the parameter estimates for reward vs. no reward trials. Subsequently, the SVC model was tested only on stimulus set II, to acquire the cross-validated decoding accuracy. These two steps were repeated with training on stimulus set II and testing on stimulus set I. We then took an average of both decoding accuracies, which gave us a measure of the locally distributed reward information of the center voxel of the searchlight. Repeating the training and testing for every possible center voxel resulted in a subject-wise, whole-brain 3D map of decoding accuracies. On the group-level, these subject-wise 3D maps were smoothed with a Gaussian Kernel of 6mm FWHM and entered into voxelwise two-sample t-tests comparing the placebo and amisulpride groups.

We also performed a conventional univariate analysis on the smoothed time series fMRI data. For this analysis, we used the same first-level design matrix comprised of the onsets for the four cue-outcome pairs and six movement regressors of no interest. For every subject, linear contrast images were computed for reward minus no reward and then taken to the group-level analyses where we used two-sample t-tests to compare the placebo and amisulpride groups.

Results and conclusions

Behaviorally, both groups could learn the cue-outcome associations during the training session and continued to perform well during the five runs in the fMRI scanner. There were no group differences in learning or performance parameters such as the percentage of correct responses, learning rate, or response times. This allowed us to compare the neural reward signals between the two groups without potentially confounding differences in behavior or learning.

Our results confirm the hypothesis that D2 receptor blockade leads to a reduction of the D2-mediated weakening of prefrontal representations and an enhancement of the pattern separation between reward and no reward. This was reflected by an in increased decoding accuracy in the amisulpride group. Specifically, the OFC showed significantly higher decoding accuracy in the

amisulpride group compared to the placebo group. Using an independent ROI analysis in anatomically defined subregions of the OFC (medial, central, and lateral OFC), we found that higher decoding accuracy, increased pattern separation, as well as greater pattern consistency across time, was exhibited specifically in the medial OFC, and not in lateral or central OFC ROIs.

Notably, the univariate analysis did not find any significant change in the mean signal for the contrast reward minus no reward in the OFC. While an exploratory univariate analysis detected elevated activity in response to reward cues in the VS in the amisulpride group, it seems that the prefrontal effect of amisulpride is more subtle, with enhanced decoding of reward information by increasing pattern separation and pattern consistency over time, independent of a change in the mean signal.

Lastly, in a post-hoc analysis, we found that amisulpride also enhanced the decoding accuracy of specific motor responses in D2 receptor dense motor areas, such as the left pre-motor (Brodmann area 6) and primary motor cortex. In contrast, there was no such increase in decoding accuracy for regions with fewer D2 receptors, such as in early visual areas.

2.3 Study 3: Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans

Background

Many disorders characterized by maladaptive reward processing, such as substance use disorders, are also marked by deficits in the DA or endogenous opioid system (Robinson and Berridge, 2008; Zald and Treadway, 2017). The incentive salience theory proposes that reward can be parsed into motivational and hedonic dimensions and that the DA and opioid systems differentially modulate these two dimensions (Berridge and Robinson, 1998; Robinson and Berridge, 1993). While the motivational dimension of reward, related to approaching the reward and working to attain the reward, relies mainly on the mesolimbic DA system, the hedonic dimension, which is related to the pleasure received from the reward, relies mainly on the endogenous opioid system. Numerous animal studies, as well as several

human studies, have provided support for this parsing scheme, and the incentive salience theory is one potential model of reward learning used to explain drug addiction and relapse (Robinson and Berridge, 2008).

Behaviorally, individuals with aberrant reward processing, such as patients with substance use disorders, often show deficits in tasks involving cue-induced responding and reward impulsivity (Dalley and Robbins, 2017; Lamb et al., 2016). Both these deficits may underlie high relapse rates and the difficulty in treating these disorders. Increased reactivity to drug-related cues may explain craving and drug taking after encountering Pavlovian cues linked with drug use even after prolonged successful abstinence. Increased reward impulsivity may explain the inability to resist the short-term reward of taking drugs, even in the face of long-term costs to health, finances, and relationships.

Several studies have provided data consistent with the idea that cue reactivity and reward impulsivity are strongly linked to drug use, maintenance and relapse. Patients struggling with addiction often show increased cue-induced responding and this increased reactivity to reward-associated cues is linked to treatment failure (Courtney et al., 2016). Similarly, reward impulsivity is also associated with an increased risk of addictive behavior as well as relapse (Brody et al., 2014; Mischel et al., 2011; Washio et al., 2011).

Both cue-induced responding and reward impulsivity are more closely related to the motivational dimension of reward than the hedonic dimension. However, past studies investigating these behaviors and their DA and opioid pharmacology have been done primarily in animal models and offer conflicting results regarding the pharmacological basis of cue-induced responding and reward impulsivity (Appendix 3, Table 1). We were therefore interested in how the DA and opioid system influence these behaviors in healthy human volunteers. Using a between-subject double-blind placebo-controlled pharmacological intervention, we investigated how a DA and an opioid blocker influenced cue-induced responding and reward impulsivity in healthy volunteers. We hypothesized that as cue-induced responding and reward impulsivity are associated with the motivational wanting dimension of reward, DA antagonism would reduce these two behaviors. As recent work has also found wanting modulations by the opioid system (Peciña and

Berridge, 2013), we expected the opioid antagonist to similarly reduce both of these behaviors.

Methods

In total 121 participants (placebo group n=40, amisulpride group n=41, naltrexone group n=40) participated in our study. Approximately 3 hours before the experimental tasks, participants swallowed a pill containing either placebo, 400mg amisulpride, or 50mg naltrexone. As described in study 2, amisulpride is a selective D2/D3-DA receptor antagonist and at the chosen dosage we expect approximately 50–80% D2 receptor occupancy. Naltrexone, on the other hand, is an unspecific opioid receptor antagonist that acts primarily on the μ- and κ-opioid receptors, with lesser and more variable effects on δ-opioid receptors. At the chosen dosage naltrexone is expected to result in >90% μ-opioid receptor occupancy. The dosages were chosen to induce comparable neurochemical responses while minimizing potential side effects. To further enhance and equate absorption of the drugs across participants, all participants were asked not to eat for at least 6 h before the start of the study.

Participants completed two tasks: a PIT task and a DD task. The PIT task was composed of three phases: an instrumental conditioning phase, a Pavlovian conditioning phase, and a transfer test phase. First, during the instrumental conditioning phase, participants learned to press a button to receive chocolate rewards. As performance improved, the reward schedule was adjusted until the performance was stable on a variable-ratio 10 schedule. Next, during the Pavlovian phase, an appetitive Pavlovian conditioned stimulus (CS+) was always paired with the receipt of a chocolate reward, while a neutral stimulus (CS-) was always paired with no outcome. Finally, in the transfer-test phase, participants encountered both the CS+ and the CS- in the absence of any rewards. During this phase, no chocolate rewards were dispensed and button pressing was recorded while the CS+ and the CS- were presented twice for 10 s in random order. To measure hunger levels, participants indicated their desire for chocolate before and after the task on a visual analog scale.

To measure DD, participants were asked to complete the Kirby (1999) Monetary Choice Questionnaire. This questionnaire is made up of 27 hypothetical

decisions in which participants select between a smaller, immediate monetary reward and a larger, delayed monetary reward. For immediate rewards, the rewards varied between 11 CHF and 80 CHF; for delayed rewards, the rewards varied between 25 CHF and 85 CHF. The delays varied between 7 and 186 days.

To control for demographic or personality differences, we also collected information about trait impulsivity through the Barratt Impulsiveness Scale (BIS-11), about differences in the Behavioral Inhibition and the Behavioral Activation System scales through the short version of the Action Regulating Emotion Systems questionnaire, and about affective responsiveness through the Affect Intensity Measure. Additionally, we measured BMI, and asked the participants about their age and education level, as well as assessed mood, in order to assess whether these factors may modulate our findings.

Results and Conclusions

The three groups did not differ in age, BMI, years of education, affect intensity, reward sensitivity or trait impulsivity. There were also no significant differences in their desire for chocolate or their learning performance during the Pavlovian and instrumental phases of the PIT task.

As expected cue-induced responding during the transfer test of the PIT task and reward impulsivity during the DD task were modulated by the pharmacological intervention. Both the DA and the opioid blocker led to a reduction in cue-induced responding during the transfer test phase of the PIT task. While the placebo group showed significant increases in the number of button presses at CS+ presentation and a significant difference between button pressing during the CS+ and the CS- presentation (corresponding to PIT), these effects were abolished in the two drug groups. Neither the amisulpride nor the naltrexone group showed increased responding to the CS+ compared to the CS-, and both groups differentiated significantly less between the two CSs than the placebo group.

The DD results were similar, albeit a bit more nuanced. Here we found that the DA blocker significantly reduced reward impulsivity compared to the placebo group. The opioid blocker also reduced reward impulsivity in comparison to the placebo group, but this reduction was not significant.

Lastly, in an explorative analysis, we examined the modulatory effect of mood on motivated behavior. Our results indicate that blocking the DA and opioid system differentially affected the association between mood and reward impulsivity. In the DA antagonist group, reward impulsivity correlated with positive mood, while in the opioid antagonist group, reward impulsivity correlated with negative mood.

3. General Discussion

3.1 Efficient encoding of reward dimensions in the PFC and VS

One approach to understanding reward processing and the circuitry involved is to parse reward into individual psychological dimensions. While animal studies have provided evidence that reward can be split into at least two dimensions – a hedonic dimension and a motivational dimension – human studies have been less definitive. In study 1 (Appendix A), we, therefore, investigated whether it is possible to dissociate these two reward dimensions in humans both behaviorally and neurally. We were able to demonstrate that it is possible, and that distinct regions in PFC consistently processed wanting (mPFC) or liking (central OFC) irrespective of which judgment type was being expressed whereas one common region in the striatum encoded one dimension or the other according to behavioral relevance.

Study 1 measured both liking and wanting in one task using identical rating scales. In contrast to previous studies in humans and animals (Pool et al., 2016), this allowed us to compare wanting- and liking-related responses directly. Most studies have used cue reactivity (Heinz et al., 2004), craving (Dagher et al., 2009; Heinz et al., 2004; McClernon et al., 2009), or hunger and pleasantness ratings (de Araujo et al., 2003; Kringelbach et al., 2003; Spetter et al., 2012) as measures of wanting and liking. These studies either did not control for the other reward dimensions or used different measures for each dimension. Accordingly, any of the findings could be related to either wanting or liking or to differences in how wanting and liking were measured. Our study substantially improves on the methodology used to assess and dissociate the two reward dimensions and allows us to investigate them in a more thorough and effective manner.

In the PFC, we observed anatomically distinct encoding of the two reward dimensions regardless of current behavioral requirements. While central OFC activity encoded liking, more medial parts of the OFC and PFC encoded wanting. The central OFC receives numerous inputs with visual, auditory, olfactory, gustatory, and somatosensory information (Kringelbach and Rolls, 2004). These sensory inputs could provide a basis for hedonic reward encoding. In contrast, the medial OFC is closely connected with the limbic system (Carmichael and Price, 1995), which in turn is often implicated in diseases marked by increased desire and wanting, such

as addiction, and has been described as the "impulsive system" (Bickel et al., 2007; Everitt and Robbins, 2005). Our data indicate that these distinct regions continue to process the motivational or hedonic value dimensions also when the present behavior is not based on them.

Compared to the PFC, in the VS, encoding of wanting and liking was anatomically less segregated and functionally more flexible, i.e. dependent on what judgment the participant was currently performing. This is in line with numerous animal studies demonstrating that wanting and liking share neural substrates in the anterior VS, with liking engaging spatially restricted areas overlapping with more distributed regions recruited by wanting (Berridge and Robinson, 2003; Berridge et al., 2009; Castro and Berridge, 2014). Critically, we find that encoding of reward dimensions in the VS flexibly switches according to what judgment is currently being evaluated. This may be a mechanism by which the striatum can reduce the cortical information it receives through cortico-striatal loops, and more efficiently pass on only the currently required information.

Reward processing in the striatum may be organized according to a dorsal-ventral divide. Popular implementations of actor-critic models (Houk et al., 1995) suggest that the dorsal striatum is important for motor and cognitive control, is a key player in the learning of stimulus-response associations, and plays the role of the actor by modifying stimulus-response associations in order to increase long-term gains (O'Doherty et al., 2004). In sum, it is critical for action selection. In contrast, the VS is thought to act as the critic and to be important for updating reward predictions (O'Doherty et al., 2004). Our findings speak to this divide, by suggesting that in parallel to the dorsal striatum's role in action selection, the VS may be key in performing value selection, by filtering value signals and passing on only information about the reward dimension that is currently relevant.

Lastly, we found that cortico-striatal connectivity strength depended on both the type of judgment that the participants were currently performing, as well as the level of wanting and liking. During liking judgments, functional connectivity between the VS and the central OFC was more strongly related to levels of liking than levels of wanting. In contrast, during wanting judgments, functional connectivity between the VS and the mPFC was more strongly related to levels of wanting. This could be a way in which activity in the VS can flexibly switch between

encoding hedonic and motivational reward dimensions depending on behavioral relevance: Functional connectivity between the VS and the specific cortical region encoding the relevant reward dimension is enhanced proportional to the level of the specific reward dimension.

In sum, our study reveals that wanting and liking of nonconsumable rewards in healthy humans can be dissociated both behaviorally and neurally, with wanting encoded in the medial OFC, mPFC, and VS, and liking encoded in the central OFC, posterior cingulate, VS, and pallidum. More importantly, we show that in contrast to the PFC, the VS encodes wanting or liking depending on which dimension is behaviorally relevant in the present situation. Thus, striatal processing of motivational and hedonic reward dimensions appears to be dynamic and particularly sensitive to ongoing behavioral requirements. Finally, the coupling between the VS and frontal regions differed according to which judgment type was behaviorally relevant, suggesting a gating function of fronto-striatal connectivity for different reward dimensions.

3.2 Dopamine modulates the stability of reward representations in the PFC

In study 2 (Appendix B), we explored reward encoding in the PFC in more detail. Specifically, we were interested in probing what the role of DA is in stabilizing and enhancing prefrontal value representations. According to the dual-state theory of prefrontal cortical networks (Durstewitz and Seamans, 2008; Seamans and Robbins, 2010), the stability as well as the flexibility of prefrontal network patterns is influenced by whether the PFC is in a D1-dominated state or in a D2-dominated state. The D1-dominated state is characterized by robust and stable network patterns; however, it is also marked by a high energy barrier between different network states, which makes representations more rigid and inflexible. In contrast, the D2-dominated state is characterized by fast and flexible switching between network patterns, due to a much lower energy barrier; however, this makes representations much weaker, noisier, and less stable. In study 2, we thus aimed to probe whether value representations in the PFC are encoded in line with the hypotheses from the dual-state theory.

We used a D2-DA receptor antagonist to induce a D1-dominated state in our participants while they performed a simple non-instrumental outcome-prediction task. To decode reward signals from the PFC we used an MVPA technique. This allowed us to look for evidence of enhanced network representations, which would result in enhanced decoding of neural reward patterns through MVPA. Consistent with the dual-state theory, we found that compared to placebo, participants who received the D2-antagonist exhibited enhanced reward representations. For the reward signals in the PFC of participants receiving the DA antagonist, there was significantly higher decoding accuracy, a greater pattern separation between the activity patterns related to reward and no reward trials, as well as a greater pattern consistency across time. This dopaminergic enhancement in the stability of reward representations was specific to medial parts of the OFC (related to wanting according to study 1; see below) and was not observed for central OFC (related to liking according to study 1).

Evidence for the dual-state theory comes primarily from animal work, but has also been supported in humans: Several studies have shown that blocking D2 receptors in the PFC impairs set shifting tasks (Floresco et al., 2006; Tost et al., 2006; Mehta et al., 2004), suggesting that the D2-system may be necessary for switching between alternatives. The flexibility of the network patterns in the D2-system would, in this case, allow for efficient updating of information, as well as allow for rapid switching between different representations, which in turn may facilitate successful performance in these types of tasks.

In contrast, D1 receptors are critical for working memory performance (Abi-Dargham et al., 2002; Constantinidis and Klingberg, 2016; Sawaguchi and Goldman-Rakic, 1991), suggesting that the D1-system may be necessary for preserving mental representations during delays. This could occur through the stable and robust network patterns in D1-dominated states, which protect representations from disturbance by noise or competing, distracting stimuli. Our finding of enhanced decoding of reward representations in the mPFC in a D1-dominated state is in line with these studies. Furthermore, by using multivariate analyses, our results suggest that a D1-dominated state stabilizes prefrontal reward representations at the level of distributed patterns (rather than more globally as with the univariate effects in the striatum).

The fact that we observe enhanced encoding accuracy of reward representations in medial OFC, and not in lateral or central OFC, is interesting considering the OFC results of study 1. The medial OFC identified in study 2 largely overlaps with wanting-related activity in the medial OFC in study 1. This could indicate that signals used to decode reward representations in study 2 may be most closely related to the motivational dimension of reward. Past studies have found mPFC activity that scales according to monetary gains and losses (Tom et al., 2007), as well as according to monetary bids on liked and disliked foods (Plassmann et al., 2010). It may be that using monetary stimuli elicits primarily wanting-related activity in the PFC, given the fact that it cannot be consumed and therefore is less directly associated with liking. However, given that the wanting signals in study 1 were much stronger than the liking signals, an alternative explanation is that liking-related activity in the central OFC was not decoded simply because of insufficient statistical power.

One limitation of our findings is that recent work suggests that parametric statistical tests may not be optimal for analyzing common measures of accuracy in MVPA methods (Allefeld et al., 2016; Stelzer et al., 2013). In study 2, we used the percentage of correct classifications as a measure of decoding accuracy. As described in detail in the methods in section 2.1, as well as Appendix 2, we determined the decoding accuracy of every voxel in the brain and performed group statistics using traditional t-tests. However, as decoding accuracy may not always be normally distributed and as the samples are not drawn from a continuous distribution, but from one bounded by zero and 100, key assumptions of the t-statistic may not be met. Furthermore, work by Stelzer and colleagues (2013) suggests that non-parametric statistics may have higher statistical sensitivity and that parametric statistics may inflate the number of false positives. It may, therefore, be useful to additionally use non-parametric statistics on our data, such as by conducting permutation testing, to validate our results.

In conclusion, using DA pharmacology and MVPA techniques, we could show that putting participants in a D1-dominated state enhanced decoding of prefrontal reward representations. This was further validated by demonstrating that participants in a D1-dominated state had a stronger pattern separation and a greater

pattern consistency across time. Our results thereby provide evidence for a role of the DA system in modulating the stability of reward representations in the PFC.

3.3 DA and opioid antagonism reduces cue-induced responding and reward impulsivity

Study 3 (Appendix C) further explored the pharmacological basis of motivational aspects of reward. Here, we considered the role of both DA and opioid pharmacology in two specific reward-related behaviors: cue-induced responding and reward impulsivity. We found that both cue-induced responding and reward impulsivity were reduced under DA blockade, and to a lesser extent under opioid blockade. Furthermore, DA and opioid antagonists differentially affected the relationship between mood and reward impulsivity: Reward impulsivity under DA blockade correlated with positive mood. In contrast, reward impulsivity under opioid blockade correlated with negative mood.

Our dopaminergic effects on cue-induced responding and reward impulsivity are in line with most animal studies and extend them to humans. Decreased PIT has been observed after inactivation of the VTA (Corbit et al., 2007; Murschall and Hauber, 2006) and administration of DA receptor antagonists (Dickinson et al., 2000; Lex and Hauber, 2008). In turn, increased PIT can be seen following administration of the indirect DA agonist amphetamine (Peciña et al., 2006; Wyvell and Berridge, 2000). Similarly, administration of the indirect DA agonists amphetamine and cocaine leads to increases in reward impulsivity (Evenden and Ryan, 1996; Helms et al., 2006; Logue et al., 1992, but see Wade et al., 2000 for contradicting results). Our findings suggest that DA plays a similar role in humans.

There have been fewer studies looking at dopaminergic effects on cue-induced responding and reward impulsivity in humans, and those that exist have all struggled with small sample sizes. One study investigated cue-induced responding in healthy volunteers and found that unspecific DA depletion reduces cue-induced responding for reward-associated cues (Hebart and Gläscher, 2015). By using a receptor type-specific intervention, our findings qualify and extend those of Herbart and Gläscher. Human studies investigating reward impulsivity have shown contradictory or null effects (Hamidovic et al., 2008; Pine et al., 2010; Wit et al.,

2002). Using a larger sample size, our results provide evidence that similar to animals, both these reward behaviors are modulated by DA antagonism in healthy human volunteers.

Reduced cue-induced responding after DA blockade is consistent with the framework of the incentive salience theory proposed by Berridge and colleagues (Berridge and Robinson, 1998). According to this theory, reward is not a unitary concept but can be parsed into separable dimensions. For instance, the motivational drive to obtain rewards (wanting) can be separated from the hedonic pleasure associated with them (liking) (Berridge and Kringelbach, 2015; Castro and Berridge, 2014; Pool et al., 2016). Animal studies have shown that motivational wanting and hedonic liking of reward can be differentiated neurochemically. While wanting relies mainly on the mesolimbic DA system, liking is mediated by the endogenous opioid system (Castro and Berridge, 2014). Since cue-induced responding is one common way to measure wanting of rewards, its reduction under DA antagonism is in line with DA's primary role in modulating wanting.

Both cue-induced responding and reward impulsivity were also reduced, although to a lesser extent, under opioid blockade. This is consistent with past studies investigating PIT (Laurent et al., 2012; Myrick et al., 2008; Peciña and Berridge, 2013), while prior studies investigating reward impulsivity offer mixed and inconsistent results (Boettiger et al., 2009; Kieres et al., 2004; Mitchell et al., 2007). Notably, the results of our study suggest that the opioid system is involved in modulating the motivational dimension of reward, as measured by cue-induced responding. Modulation of wanting through manipulations of the opioid system has been observed in the past (Castro and Berridge, 2014; Peciña, 2008; Peciña and Berridge, 2013). However, due to the close interrelation between the DA and opioid system, it is difficult to determine conclusively whether the effect on wanting is driven solely by modulation of the opioid system or by interactions between the opioid and DA systems.

Lastly, we find that the relationship between mood and reward impulsivity was differentially affected by the drug group. Specifically, we found that in the DA antagonist group there was a positive relationship between mood and reward impulsivity: Participants that reported higher positive mood also acted more impulsively. In contrast, we found that in the opioid antagonist group this

relationship was reversed: Participants that reported higher positive mood acted less impulsively. This may indicate that mood should be considered when prescribing medications to reduce symptoms of enhanced reward impulsivity. Patients with low moods may benefit more from DA antagonists than opioid antagonists and vice versa. However, since our mood measure was only taken at the end of the study with no baseline comparison, it is a relatively crude measure. Future studies are necessary to replicate our findings and confirm this interaction effect of drug, mood, and impulsivity.

Taken together, our results of decreased cue-induced responding and reward impulsivity under both DA and opioid blockade are largely in line with previous animal studies and extend them to humans. This suggests that both the DA and the opioid system are involved in processing motivational dimensions of reward as described in the incentive salience theory. Additionally, our findings of stronger reductions in both behaviors under DA antagonism implies that it may be most promising to focus on the DA system when treating disorders marked by maladaptive reward processing. Finally, it may be worthwhile to take a closer look at inter-individual differences, such as in mood, when studying the pharmacological basis of reward processing, to gain a more fine-tuned understanding of how individual patients may respond to different treatments.

4. General Conclusions

Numerous studies in the past decade have investigated how rewards are processed in the brain. Notably, many different types of rewards, be it primary, secondary, or even social rewards, and numerous types of tasks, from passive viewing to decision making, have produced surprisingly similar results. Searching the brain for activity that scales either with the size of the reward or the participant's subjective valuation consistently identifies the OFC, mPFC, VS, and posterior cingulate (Grabenhorst and Rolls, 2011; Kable and Glimcher, 2009; Padoa-Schioppa, 2011; Platt and Huettel, 2008; Rushworth, 2008; Wallis, 2011). However, how the vast amount of reward-related information is encoded in the brain is still largely unclear.

Our results shed light on this question and provide evidence for one potential mechanism how different reward dimensions may be efficiently encoded in the

brain. Study 1 suggests that different dimensions of reward are encoded in the PFC in an anatomically segregated manner regardless of task demand. Study 2 provides evidence of dopaminergic enhancement of the stability of prefrontal reward representations. Taken together, this could suggest that the PFC is important in encoding reward dimensions in parallel, and that DA (especially the D1-system) ensures the stability and robustness of these segregated signals. Subsequently, only behaviorally relevant prefrontal value signals may be passed on to cortico-striatal pathways, allowing for an effective way to reduce the complexity of the reward information that reaches the VS. Through enhanced connectivity between the VS and those cortical areas encoding the currently relevant reward dimension, only the presently required reward information is processed further.

The idea that the PFC, and especially the OFC, may be functionally organized according to specific reward dimensions, valence, or tasks, is not new. Both monkey recording and human imaging studies have indicated that there is a medial-lateral divide in the OFC. Most evidence suggests the OFC is organized according to a valence gradient, with medial OFC processing affectively positive stimuli and rewards, and lateral OFC processing affectively negative stimuli and punishments (Kringelbach and Rolls, 2004; Liu et al., 2011; O'Doherty et al., 2001). However, alternative accounts have also been proposed, such as that the organization of the OFC may rely on the type of value computation that is being performed (Rich and Wallis, 2014). Our findings inform this debate by providing evidence that the OFC may be important for encoding different reward dimensions in anatomically distinct regions, and that DA may function as a stabilizer to maintain robust and separate prefrontal reward representations.

In our last study, we took a closer look at two reward-related behaviors: cue-induced responding and reward impulsivity. Both cue-induced responding and reward impulsivity are thought to contribute to the initiation and maintenance of compulsive behaviors, as well as to relapse after treatment or therapy. We find that both DA and opioid pharmacology modulates cue-induced responding and reward impulsivity: Blocking DA or opioid receptors leads to a reduction in reward seeking and impulsive behavior. Considering our previous results regarding neural reward encoding, it could be that putting subjects in a D1-dominated state, which leads to enhanced and stable reward signals, drives these effects. Especially concerning

reward impulsivity, these enhanced and stable signals may make it easier for subjects to detect the highest value alternative without being distracted by the attractiveness of short time delays.

In conclusion, our results suggest that reward information is encoded in distributed and separate areas in the PFC and that only behaviorally relevant reward information is represented in the VS. Furthermore, the D1-DA system may enhance the stability of prefrontal reward representations, and aberrant reward processing, such as increased impulsivity, may be driven by deregulation of the DA system – potentially by deregulation of the D1-D2-system balance. This has important implications for how we characterize disorders related to aberrant reward processing and how we think about treatment for these disorders. In the end, we hope that neural and pharmacological investigations of hedonic and motivational reward dimensions will help both individuals dealing with compulsive or diminished reward seeking, as well as help the healthy align their motivations and pleasures so that rewards that are liked are sought out and those that are sought out are liked.

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List of Abbreviations

ACC – anterior cingulate cortex
BDM – Becker-DeGroot-Marschak (auction)
CHF – Swiss franc
CS – conditioned stimulus
DA – dopamine
DD – delay discounting
fMRI – functional magnetic resonance imaging
GLM – general linear model
mPFC – medial prefrontal cortex
MVPA – multivoxel pattern analysis
NAc – nucleus accumbens
OFC – orbitofrontal cortex
PIT – Pavlovian-instrumental transfer
PFC – prefrontal cortex
PPI – psychophysiological interaction
ROI – region of interest
SVC – support vector classification
VS – ventral striatum
VTA – ventral tegmental area
vmPFC – ventromedial prefrontal cortex

Appendices

A. Appendix to Study 1

Fronto-striatal pathways gate processing of behaviorally relevant reward dimensions

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Abstract

Rewards vary on multiple affective and motivational dimensions. Reward-encoding brain regions such as the ventral striatum (VS) are known to process these dimensions. However, the mechanism whereby reward dimensions are selected for neural processing and guiding behavior remains unclear. Therefore, we investigated how human individuals made either hedonic (liking) or motivational (wanting) evaluations of everyday items while undergoing functional imaging. We found that activity in the VS encoded both hedonic and motivational dimensions of reward. Critically, the VS preferentially processed the dimension currently being evaluated and showed judgment-specific functional connectivity with areas in the prefrontal cortex that encoded hedonic and motivational dimensions of reward, regardless of which judgment was currently relevant for behavior. These findings suggest a gating mechanism by which fronto-striatal pathways flexibly encode reward dimensions depending on their behavioral relevance. These findings have implications for impairments in behavioral flexibility observed in obsessive-compulsive disorder, addiction, and schizophrenia.

Introduction

Reward is central for goal-directed behavior. However, reward is not a unitary concept but characterized by multiple dimensions. Activity in reward processing regions such as the ventral striatum (VS) correlates with various reward dimensions, including gains and losses (Delgado et al., 2000), pleasantness (Blood and Zatorre, 2001), hedonic value (Pecina and Berridge, 2005), motivational value (Kahnt and Tobler, 2013; Nunes et al., 2013), expected value (Knutson et al., 2005; Tobler et al., 2007), received value (Elliott et al., 2003), decision value (Lim et al., 2011), and salience (Zink et al., 2004). Some of these different reward dimensions can be separated at the behavioral level (Kahneman et al., 1997; Berridge et al., 2009). This raises an important yet unresolved question: does the VS process these dimensions simultaneously and in parallel, irrespective of which dimension is currently relevant for behavior? Alternatively, if instead of parallel processing only one dimension is processed at a time, how does the VS selectively and flexibly gate access to the behaviorally relevant signals?

Here we focus on two particular reward dimensions, which overlap anatomically in the VS: the motivational drive to obtain rewards (wanting) and the hedonic pleasure associated with rewards (liking) (Castro and Berridge, 2014; Berridge and Kringelbach, 2015; Pool et al., 2016). Given the overlap of wanting and liking within the VS (Berridge and Robinson, 2003; Berridge et al., 2009; Castro and Berridge, 2014) and the VS's central position at the center of cortico-striatal loops (Haber, 2011), either mechanism could be implemented. The VS could participate in largely separate and parallel wanting and liking loops (Alexander et al., 1986; Cummings, 1993), passing on information received from distinct regions in medial prefrontal and orbitofrontal cortex. In contrast, based on the anatomical convergence of prefrontal projections in the VS (Ferry et al., 2000; Haber et al., 2006), the VS could dynamically interact with cortical wanting and liking regions depending on which dimension is currently required for guiding behavior.

The present study probes whether the VS processes wanting and liking in parallel or flexibly encodes the dimension that is behaviorally relevant in a given moment. We designed a task in which participants indicated how much they wanted or liked various non-consumable rewards. If the VS processes both dimensions in

parallel, activity should scale with wanting or liking ratings irrespective of whether the current judgment is a wanting or a liking judgment. Conversely, if the VS gates signaling depending on the behaviorally relevant reward dimension, then VS activity should primarily encode the dimension that has to be judged in the current trial. In this case, activity in VS should reflect wanting ratings during wanting judgments and liking ratings during liking judgments. In agreement with the second hypothesis, we find evidence for striatal gating of hedonic and motivational reward dimensions. In contrast to the coding specificity observed in the VS, distinct regions of medial prefrontal and orbitofrontal cortex encoded wanting or liking regardless of judgment type. Finally, fronto-striatal connectivity varied as a function of judgment type, supporting the idea that access to the currently relevant reward dimension is gated in the striatum.

Results

Wanting and liking can be dissociated behaviorally

Participants rated everyday items in the scanner according to how much they *wanted* and how much they *liked* them (Figure 1A & B). The ratings in the scanner were collected twice – once before and once after participants played a game in which they won half of the items, which were handed over to them at the end of the game. The game allowed us to separate wanting and liking behaviorally, while also making the task more engaging.

Participants differentiated between wanting and liking judgments regarding response times and ratings (Figure 1C-E). An ANOVA with repeated-measures factors *Session* (pre or post game), *Judgment type* (wanting or liking rating), and *Stimulus type* (won or lost item) revealed a main effect of Session on response times ($F(1,27)=29.94$, $p<0.0001$), as well as a main effect of *Judgment type* ($F(1,27)=41.10$, $p<0.0001$). Participants took significantly more time to make liking judgments than wanting judgments ($t(27)=6.39$, $p<0.001$; Figure 1E), suggesting that participants treated the two judgment types differently. Furthermore, wanting and liking ratings changed differentially from pre to post depending on whether the item was lost or won. Specifically, an ANOVA with repeated-measures factors *Judgment type*

(wanting or liking rating) and *Stimulus type* (won or lost item), revealed both main effects of *Judgment type* ($F(1,27)=10.49$, $p<0.005$) and *Stimulus type* ($F(1,27)=21.40$, $p<0.0001$), as well as an interaction between *Stimulus* and *Judgment type* on the change in ratings from pre to post game ($F(1,27)=34.50$, $p<0.0001$). Wanting decreased specifically for won items (change in wanting won vs. lost items: $t(27)=-5.28$, $p<.001$; wanting won pre vs. won post: $t(27)=4.81$, $p<0.001$; wanting lost pre vs. lost post: $t(27)=-0.16$, $p=0.873$; Figure 1C). In contrast, liking decreased specifically for lost items (change in liking won vs. lost items: $t(27)=2.79$, $p<0.05$; liking won pre vs. won post: $t(27)=0.52$, $p=0.609$; liking lost pre vs. lost post: $t(27)=4.50$, $p<0.001$; Figure 1D). Taken together, these differences in response times and ratings provide evidence that the participants could differentially process the wanting and liking of items.

Neural activity in the orbitofrontal and medial prefrontal cortex correlates with either wanting or liking

We next assessed which neural systems encoded wanting and liking. Using a parametric general linear model (GLM), we identified regions where activations were parametrically associated either with wanting or with liking ratings (Table 1, Figure 2). In this GLM, we pooled data from both liking and wanting trials, resulting in one onset regressor, which was modulated by three parametric modulators (PMs): the individual average wanting rating of the presented item, the individual average liking rating of the presented item, and the trial-specific response time (serial orthogonalization of parametric regressors was turned off for these analyses (Mumford et al., 2015)). In a whole-brain (voxel-level) corrected analysis, we found that wanting was related to prefrontal activations, including medial parts of the orbitofrontal cortex (OFC; $z=5.03$, family-wise error (FWE)-corrected, $p<0.05$, peak [0, 50, −5]; Figure 2A), and the medial prefrontal cortex (mPFC; $z=5.21$, FWE-corrected, $p<0.005$, peak [−3, 44, −2]). In contrast, liking-related responses were more focal and limited to the central OFC ($z=4.86$, FWE-corrected, $p<0.05$, peak [−24, 47, −14]; Figure 2G) and posterior cingulate ($z=4.92$, FWE-corrected, $p<0.05$, peak [0, -34, 25]). These results suggest that neural activity in anatomically segregated regions of the PFC track either wanting or liking.

To further characterize the degree to which these responses are specific to wanting or liking, we employed a post-hoc regions-of-interest (ROI) analysis. We extracted both liking- and wanting-related responses in the clusters associated with wanting and liking ratings (Table 1) and assessed the difference between these responses. This allowed us to determine whether different regions encoded wanting and liking differently or similarly. While wanting- and liking-related responses in the posterior cingulate ROI did not differ significantly ($t(27)=1.79$, $p=0.084$), those extracted from the medial OFC and mPFC ROIs did. Responses in the central OFC showed significantly stronger associations with liking than wanting ($t(27)=2.62$, $p=0.014$). In contrast, the medial OFC cluster as well as the mPFC cluster showed significantly larger responses for wanting than liking (medial OFC: $t(27)=-2.97$, $p=0.006$; mPFC: $t(27)=-3.91$, $p=0.001$). Thus, wanting and liking appear to be processed in anatomically distinct regions in the PFC but overlap in the posterior cingulate.

Neural Activity in common regions of the VS correlates with both wanting and liking

Previous animal work has implicated the VS (nucleus accumbens) and the pallidum in encoding both wanting and liking (Pecina et al., 2006). Based on these findings, we examined the role of these two areas in more detail. We analyzed data in two *a priori* anatomically defined ROIs encompassing these two regions (Table 1, Figure 2). In the VS, we found wanting-related activations ($z=4.06$, small volume correction (FWE-SVC), $p<0.01$, peak [-6, 11, −2]; Figure 2B), as well as more confined liking-related activations ($z=3.79$, FWE-SVC, $p<0.05$, peak [-9, 14, −5]; Figure 2H). In the pallidum, activity was parametrically associated only with liking ratings ($z=3.97$, FWE-SVC, $p<0.01$, peak [-15, 5, −2]). Thus, in line with previous animal studies, we find the VS encoded both wanting and liking, whereas the pallidum seems to be involved primarily in processing liking.

To more systematically assess the relation of these striatal and pallidal responses to wanting and liking, we extracted and compared both wanting- and liking-related responses from the clusters in the VS and pallidum (Table 1). In contrast to the PFC clusters but similar to the posterior cingulate cluster, comparable wanting- and liking-related responses were found in both the VS and

pallidum ROIs associated with liking (VS: t(27)=0.67, p=0.508; pallidum: t(27)=1.05, p=0.305), as well as the VS ROI associated with wanting (VS: t(27)=-1.18, p=0.249). In line with an overlap of both reward dimensions primarily in the VS, a formal conjunction analysis (Nichols et al., 2005) revealed common wanting and liking areas in the VS (z=3.97, FWE-SVC, p<0.05, peak [-9, 11, −5]; Figure 3A), but not in the pallidum and the posterior cingulate. Thus, while prefrontal responses appear to be specific to either wanting or liking and exhibit a regional dissociation between the two, responses in the VS (and to a lesser degree in the pallidum and posterior cingulate) seem to commonly encode both reward dimensions.

Striatum, but not PFC, encodes reward dimensions in a behaviorally-relevant manner

The results reported above suggest that wanting and liking are encoded in overlapping regions in the striatum but in separate regions in the PFC. We next assessed whether encoding of these two dimensions in the VS depends on which dimension is currently relevant for behavior. We, therefore, tested whether the responses identified by the parametric GLM were independent of the type of judgment participants made in a given trial or whether the VS switched between coding wanting and liking as a function of judgment type. For this analysis, we used a second parametric GLM that was split by trial type, with two regressors corresponding to trials in which liking and wanting judgments were made, respectively. Each of these regressors was again parametrically modulated by the individual average wanting rating of the presented item, the individual average liking rating of the presented item, and the trial-specific response time (serial orthogonalization of parametric regressors was again turned off for these analyses (Mumford et al., 2015)). These analyses were performed in ROIs of 6mm spheres around the peak voxels from the first parametric GLM (Table 1). We extracted and compared wanting-related responses during wanting and liking trials as well as liking-related responses during wanting and liking trials. This allowed us to assess whether responses were specific to the currently performed judgment (e.g., for wanting, specificity would be reflected in significantly stronger wanting signals emitted by wanting-related regions from the first model during wanting judgments compared to liking judgments).

For both liking- and wanting-related responses, areas in the PFC and posterior cingulate encoded reward dimensions irrespective of judgment type. Specifically, we found that liking-related responses within the central OFC ROI were significant during both liking and wanting judgments (liking trials: $t(27)=2.83$, $p=0.009$; wanting trials: $t(27)=2.15$, $p=0.041$) and did not differ significantly between judgment types (liking vs. wanting trials: $t(27)=0.45$, $p=0.655$). Likewise, liking-related responses in the posterior cingulate were significant during both judgment types (liking trials: $t(27)=4.41$, $p= 0.0001$; wanting trials: $t(27)=4.14$, $p= 0.0003$) and did not differ significantly (liking vs. wanting trials: $t(27)=0.23$, $p=0.823$). Moreover, wanting-related responses in the mPFC and medial OFC were significant during both wanting and liking trials and did not differ significantly between judgment types (mPFC: wanting trials: $t(27)=4.83$, $p=0.00005$; liking trials: $t(27)=4.57$, $p=0.0001$; wanting vs. liking trials: $t(27)=0.12$, $p=0.903$; medial OFC: wanting trials: $t(27)=5.33$, $p=0.00001$; liking trials: $t(27)=4.15$, $p=0.0003$; wanting vs. liking trials: $t(27)=0.51$, $p=0.613$). Thus, beyond exhibiting regional specificity for motivational versus hedonic reward dimensions, these anatomically segregated cortical regions also appear to consistently code wanting or liking, regardless of which judgment is currently being made.

In contrast, responses in the VS strongly depended on the current judgment type. Liking-related responses in the VS were only significant during liking judgments (liking trials: $t(27)=4.85$, $p=0.00005$; wanting trials: $t(27)=1.49$, $p=0.15$) and significantly stronger during liking than wanting judgments (liking vs. wanting trials: $t(27)=2.32$, $p=0.028$). Similarly, wanting-related responses in the VS were only significant during wanting judgments (wanting trials: $t(27)=3.61$, $p=0.001$; liking trials: $t(27)=1.27$, $p=0.216$) and significantly stronger for wanting than liking judgments (wanting vs. liking trials: $t(27)=2.80$, $p=0.009$). Focusing on the activation pattern of the common overlapping voxels in the VS (Figure 3A) mirrored this finding. We compared wanting-related and liking-related signals in the VS cluster defined by the conjunction analysis using an ANOVA with repeated-measures factors *Judgment type* (wanting or liking trial) and *Parametric modulator type* (wanting or liking). In line with selective processing of the currently relevant reward dimension, we found a significant interaction of both factors ($F(1,27)=7.17$, $p=0.012$; Figure 3B), with stronger wanting-related responses during wanting

judgments than liking judgments ($t(27)=2.53$, $p=0.018$), and stronger liking-related responses during liking than wanting judgments ($t(27)=2.28$, $p=0.031$). Taken together, while the frontal ROIs (OFC and mPFC) exhibit regional specificity for wanting and liking regardless of judgment type, the striatum flexibly encodes wanting or liking depending on whether wanting or liking judgments are required.

Fronto-striatal pathways gate behaviorally relevant reward dimensions

Lastly, we explored the mechanism by which activity in the VS could flexibly switch between the encoding of different reward dimensions. One possible mechanism could be to flexibly enhance the cross-talk between the VS and the cortical region processing the currently relevant dimension proportional to the current level of this reward dimension. To examine this possibility, we performed a psychophysiological interaction (PPI) analysis and tested whether functional coupling (fMRI signal coherence) between the VS and wanting and liking regions in the PFC depended on the type and level of the current judgment. We used the overlapping voxels in the VS as a seed region to extract the physiological signal. Psychological factors were liking and wanting judgment trials, each parametrically modulated by the average wanting and liking ratings of the current item. The parametric modulators were multiplied by the physiological variable to generate a total of 4 psychophysiological regressors (liking trial liking rating, liking trial wanting rating, wanting trial liking rating, wanting trial wanting rating). As target regions, we focused on the same ROIs in central OFC and mPFC defined above that processed wanting and liking ratings irrespective of the current judgment. During liking judgments, we found that VS connectivity with the central OFC was more strongly related to levels of liking than levels of wanting ($z=3.26$, FWE-SVC, $p<0.05$, peak [-21, 44, −11]; Figure 3 C). Conversely, during wanting judgments we found that VS connectivity with the mPFC was more strongly related to levels of wanting than levels of liking ($z=3.10$, FWE-SVC, $p<0.05$, peak [-6, 44, 4]; Figure 3C). These results indicate that flexible processing of reward dimensions in the VS is realized by selectively gating input from regions of the PFC that encode the reward dimension that is currently relevant for behavior. Moreover, the degree of this connectivity modulation is directly related to the level of the currently relevant reward dimension.

Discussion

A key contribution of our study is to clarify the role of the striatum in different dimensions of reward processing. We found that the striatum, in contrast to prefrontal regions, flexibly encodes reward dimensions depending on what is currently behaviorally relevant. This provides important insight into how reward information may be transformed in cortico-striatal circuits. The functional and anatomical nature of these circuits has been the focus of substantial amount of research. While earlier animal studies had suggested mainly a segregated, independent and parallel processing of information (Alexander and Crutcher, 1990; Selemon and Goldman-Rakic, 1985), recent models of how information is processed in the cortico-striatal loops have proposed a more integrative role for the striatum, where information from the cortex converges in the striatum and only behaviorally relevant information is passed on (Frank, 2011; Houk et al., 1995; Houk and Wise, 1995; Percheron and Filion, 1991; Bar-Gad et al., 2003). Our results support the latter hypothesis, as we demonstrated that the VS preferred to encode the currently relevant reward dimension.

In contrast to the common coding of wanting and liking in the VS according to behavioral relevance, we find anatomical specificity in the cortical encoding of reward dimensions irrespective of behavioral relevance. Thus, the PFC appears to process the two reward dimensions studied here in a segregated and parallel manner. Specifically, we demonstrate that the motivational aspect of reward is processed by medial parts of the OFC, while the hedonic aspect is processed by the central/lateral OFC. A similar medial-lateral distinction has been observed in prior animal recording and human imaging studies, with medial frontal regions exhibiting a role in goal-directed calculations (Rushworth et al. 2013), and lateral frontal regions being more strongly involved in encoding emotion and affective values of specific outcomes (Kringelbach, 2005; Kringelbach and Rolls, 2004; Murray, 2007; Rushworth et al., 2011; Howard et al., 2015; Howard and Kahnt, 2017). Our results extend this literature, by demonstrating that not only are areas of the PFC anatomically segregated in function but that they also process reward information in a parallel and consistent manner, irrespective of the current behavioral requirements.

Our findings are in line with the notion that information about distinct reward dimensions is segregated in the cortex, then converges onto the striatum and is expressed according to which type of value judgment is required. Thereby, our data inform current models of basal ganglia function and suggest how the basal ganglia can select appropriate actions while facing a considerable convergence of cortical information (Frank, 2011; Bar-Gad et al., 2003). Our data also suggest that flexible changes in VS encoding of reward dimensions are mediated by changes in the regionally corresponding allocation of fronto-striatal connectivity, with the strength of VS connectivity with specific regions in PFC being directly related to the level of the currently processed reward dimension. This is neurobiologically plausible, as the striatal spiny neurons receive input from numerous cortical neurons and can use pattern recognition to detect what is currently behaviorally relevant to the individual (Houk et al., 1995; Houk and Wise, 1995; Haber et al., 2006; Lawrence et al., 1998). In fact, behaviorally specific striatal single unit activity has been demonstrated for motor programs (Mink, 1996). Mechanistically, the striatal spiny neurons could, therefore, fire to signal-relevant cortical value input, which could lead to a pause in firing in the pallidum and in turn produce specific activity for appropriate initiation of an action. Additionally, striatal dopamine may support the gating and control of cognitive representations from the PFC (Cools, 2011). Together, whereas our data indicate that the striatum may play a key role in information selection by gating cortical inputs, the pharmacological underpinnings of the behaviorally-relevant encoding of reward dimensions require further investigation.

Conceptually, flexible encoding of specific reward dimensions in the VS may more closely reflect the explicit decision of the individual than judgment-independent segregated reward signals in the cortex. While this finding is in conflict with studies finding pre-decision valuation signals also in the striatum (Kable and Glimcher, 2007; Rangel et al., 2008), many studies do link the striatum with action selection (van der Meer and Redish, 2011). In fact, the VS is vital for motivating actions and behaviors (Berridge and Robinson, 1998; Mogenson et al., 1980), and has been found to influence action selection, by being involved in the choice, execution and inhibition of decisions and behaviors (Berridge, 2007; Cardinal et al., 2002; Nicola, 2007; Salamone et al., 2009). Our study used current behavioral

relevance as a tool to further investigate and separate signals in the PFC and VS. The results suggest that cortical valuation signals may act as inputs in the choice process, whereas striatal signals are more closely related to the outcome of the decision or action-appropriate value selection.

Our findings of common wanting and liking signals in the VS are in line with numerous animal studies investigating hedonic and motivational reward dimensions (Tindell et al., 2005; Wyvell and Berridge, 2000; Pecina and Berridge, 2005; Pecina et al., 2006; Smith and Berridge, 2007). Similarly, human neuroimaging studies using dietary restraint and satiation have found both wanting and liking signals in the VS (Born et al., 2011; Jiang et al., 2015). In the light of these studies, our current finding of behavioral relevance-dependent expression of wanting in the VS suggests that behavioral relevance of wanting judgments for food rewards may be modulated by satiety and dietary restraint.

Cortical reward signals have been linked to both hedonic and motivational dimensions of reward. In rats, Mena and colleagues (2011) found that local administration of a mu-opioid receptor agonist in the OFC and mPFC (corresponding to the infralimbic and prelimbic cortex) led to increased food intake. In humans, the OFC is often identified as an important reward and pleasure center, with medial and central parts of the OFC responding to pleasant tastes and smells (de Araujo et al., 2003; Howard et al., 2015), to monetary (O'Doherty et al., 2001) and implicit and explicit social rewards (Tobler et al., 2016; Preller et al., 2014), as well as to pleasant musical chords (Blood et al., 1999). Particularly medial and more dorsal regions of OFC, extending into anterior cingulate and medial PFC have also been associated with processing decision value (La Vega et al., 2016; Sokol-Hessner et al., 2012; Howard and Kahnt, 2017; Howard et al., 2015), which is directly related to how much a choice alternative is wanted (Rangel and Clithero, 2013; Montague and Berns, 2002). In line with this view, we and others find wanting signals in the medial OFC (Jiang et al., 2015), as well as vmPFC (Heinz et al., 2004; Lawrence et al., 2012; Smith et al., 2010). Notably, our findings indicate that choice is not necessary to reveal value-related responses in these regions, concurring with previous findings that the brain valuation system is engaged in valuation even when there are no economic choices (Gross et al., 2014; Lebreton et al., 2009; Levy et al., 2011; Smith et al., 2014; Tobler et al., 2008; Tusche et al., 2010). More importantly, we go beyond

previous findings by revealing that wanting-related parametric value levels activate the mPFC more than liking-related value levels and thereby specify the function of this core component of the valuation system.

Finally, dysfunctions in fronto-striatal loops are implicated in several neuropsychiatric disorders such as obsessive-compulsive disorder, addiction, and schizophrenia. For example, addiction could be viewed as a wanting-dominated state (Berridge et al., 2009) where the behaviorally appropriate switching to liking no longer works. Our results suggest that this may be due to altered fronto-striatal coupling. More generally, our findings may have implications for these impairments and may ultimately help to develop novel treatment approaches.

Conclusions

We find anatomically segregated wanting and liking-related signals in the PFC, as well as common wanting and liking-related responses in the VS. Our results are consistent with the idea that hedonic and motivational reward dimensions from the cortex converge in the striatum and are passed on from the striatum in a condensed and focused manner. We suggest that this is mechanistically implemented through fronto-striatal gating of different reward signals. In the PFC, motivational and hedonic dimensions of reward are encoded in a parallel and anatomically separated manner, while the VS flexibly encodes only the reward dimension that is currently relevant for behavior. This allows the striatum to act as a detector for behaviorally relevant reward dimensions and enables selective processing of reward information required for guiding ongoing actions appropriately. Thus, our findings show how the VS reduces the multiplexed nature of reward information and enables adaptive action selection. More generally, we demonstrate that besides selecting actions that provide the highest (decision) value within a given situation, the brain can also contextually select value representations. Finally, our data suggest situation-adapted modulation of connectivity as one possibility of achieving selection.

Materials and methods

Participants

We studied 28 right-handed participants, aged 20-29 years (22.8 ±0.5 years, mean ±SEM; 14 females). All participants were recruited from the *Laboratory for Social and Neural Systems Research* participant pool and provided written informed consent. The study was approved by the ethics committee of the Canton of Zurich.

Design and Procedure

Forty everyday items were used as rewards in the study. Items were selected based on prior pilot experiments, so that initial mean liking and wanting ratings were similar. Before scanning, participants viewed all items in real life, which ensured that they recognized and were familiar with each item. During the tasks, pictures of items were presented using Matlab (MathWorks Inc.) and the Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php).

In the scanner, participants were asked to rate each item according to how much they *wanted* to have it, as well as how much they *liked* the item, at that moment. In each trial (Figure 1B), participants first saw a cue indicating the type of rating trial (1s), followed by an image of the item (3s), and finally the rating screen (3.5s). Ratings were provided on a continuous scale using a trackball. Trials were separated by a variable inter-trial-interval (mean 3s). Each item was rated twice for wanting and twice for liking, resulting in 160 trials split into 4 runs before the game and the same again after the game.

Participants performed the rating task in two sessions, which were separated by a game in which participants could win some of the items outside of the scanner (Figure 1A). The game consisted of a perceptual task, in which participants had to indicate whether the item was presented to the left or the right of the midpoint of the screen. Participants won items that they classified correctly. The difficulty of the game was calibrated so that participants won and lost 50% of the items. In order to make the items more salient and thereby enhance the memorability of winning and losing the items, participants were seated at a table with the items set up next to them, while they performed the task on a computer. Additionally, immediately after

the game, participants packed up the items they won in a bag, which they later took home.

MRI Data Acquisition

Whole-brain scanning was performed with a Philips Achieva 3T whole-body MRI scanner equipped with an 8-channel head coil. For each of the 8 scanning runs, 227 T2*-weighted whole-brain EPI images were acquired in ascending order (33 transverse (axial) slices per volume, Field of View 192x192x108 mm, slice thickness 2.6 mm, 0.7 mm gap, in-plane resolution 2×2 mm, matrix 96*96, repetition time (TR) 2000 ms, echo time (TE) 25 ms, flip angle 80°). Additionally, a T1-weighted turbo field echo structural image was acquired in sagittal orientation for each participant with the same angulation as applied to the functional scans (181 slices, Field of View 256x256x181 mm, slice thickness 1 mm, no gap, in-plane resolution 1*1 mm, matrix 256*256, repetition time 8.4 ms, echo time 3.89 ms, flip angle 8°).

MRI Preprocessing

Preprocessing and statistical analysis of the MRI data was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Trust Centre for Neuroimaging, London, UK). All EPI images were temporally corrected to the middle slice, realigned to the mean image, normalized (resampling to 3×3×3 mm voxels) to the standard EPI template of the Montreal Neurological Institute (MNI) and smoothed using a Gaussian Kernel with 4 mm full width at half maximum (FWHM). We chose a relatively small smoothing kernel, as we were particularly interested in the VS and a recent meta-analysis found that in order to avoid bias against subcortical activations, applying minimal smoothing is recommended (Sacchet and Knutson, 2013).

MRI Data Analysis

To detect activity related to wanting or liking, we used a parametric analysis. The first GLM pooled data from wanting and liking judgments into one judgment-type-unspecific regressor, time-locked to the onset of each trial. This regressor was modulated by 3 parametric modulators (PMs): within-session normalized average wanting ratings, within-session normalized average liking ratings, and response

times. Importantly, to ensure that all regressors explain only independent components of variance, serial orthogonalization of parametric regressors (as implemented in SPM) was turned off (Mumford et al., 2015). Moreover, the GLM contained the 6 nuisance movement parameters. The duration of the onset regressor was 7s, which corresponds to the time participants had to view and rate each image (Figure 1B). We report whole-brain results ($p<0.05$, voxel-level family-wise error (FWE) corrected) as well as activations in the *a priori* ROIs ventral striatum and pallidum ($p<0.05$, voxel-level FWE corrected). The ROI for the VS was based on earlier studies and included the nucleus accumbens, ventral caudate nucleus, and putamen rostral to the anterior commissure (Murray et al., 2008). The ROI for the pallidum was derived from the automatic anatomical labeling (AAL) atlas incorporated in the WFU-PickAtlas Tool in SPM (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002).

In order to determine whether responses were specific or common to wanting and liking we used an ROI analysis. To check for specificity, we extracted parameter estimates for each of the wanting and liking clusters identified by the parametric contrast (table 1) and used paired t-tests to determine whether parameter estimates of one PM were significantly higher than the other PM. To determine common areas of wanting and liking we used an inclusive masking procedure, which identifies areas significantly associated with both wanting and liking PMs (Nichols et al., 2005).

We used a second GLM to investigate judgment-specific and judgment-unspecific activations. In this model we separated wanting and liking trials, so that there were two onset regressors corresponding to judgment type (wanting trial or liking trial), which each had 3 parametric modulators associated with it (within-session normalized average wanting ratings of the presented item, within-session normalized average liking ratings of the presented item, and trial-specific response times), as well as the 6 nuisance movement parameters. Again, serial orthogonalization of parametric regressors was turned off. We then used an ROI analysis to investigate whether responses to wanting and liking identified by the first GLM depended on judgment type. ROIs were 6mm spheres around the peak of the activations identified by the first GLM. We used Marsbar (Brett et al., 2002; http://marsbar.sourceforge.net/) to extract parameter estimates for each of the

PMs split by judgment type, which were then tested using repeated-measures ANOVAs and paired t-tests.

Connectivity Analysis

We performed a PPI analysis (Friston et al., 1997) with the VS (showing common coding of wanting and liking) as the seed region and *Judgment type* (wanting vs liking) and *Level* (parametric regressors for wanting vs liking ratings) as psychological factors. We used the generalized form of the PPI model (McLaren et al., 2012) to test whether the strength of the functional connectivity between the VS and the cortical regions showing specific coding of either wanting or liking depended on the type and level of the judgment performed on a given trial. The seed region was defined by the overlap of the wanting and liking-related activations (Figure 3A). For each subject, we estimated a PPI model with the activity in the seed region included as the physiological regressor and *Judgment type* (wanting trial or liking trial), modulated by the within-session normalized average wanting ratings, as well as the within-session normalized mean liking ratings included as the psychological regressors. The four parametric modulators were multiplied with the physiological variable to create the psychophysiological regressors of interest (liking trial liking rating, liking trial wanting rating, wanting trial liking rating, wanting trial wanting rating). The two critical comparisons of the PPI regressors were: wanting rating vs liking rating during wanting trials and liking rating vs wanting rating during liking trials. We focused our analysis on the prefrontal clusters in the mPFC and OFC that were identified by the first GLM.

Acknowledgments

This work was supported by the Swiss National Science Foundation (PNT: PP00P1_150739 and 00014_165884, BBQ: PP00P1-123516/1 and PP00P1-146326/1). We thank Karl Treiber for help with data collection.

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Figures and tables

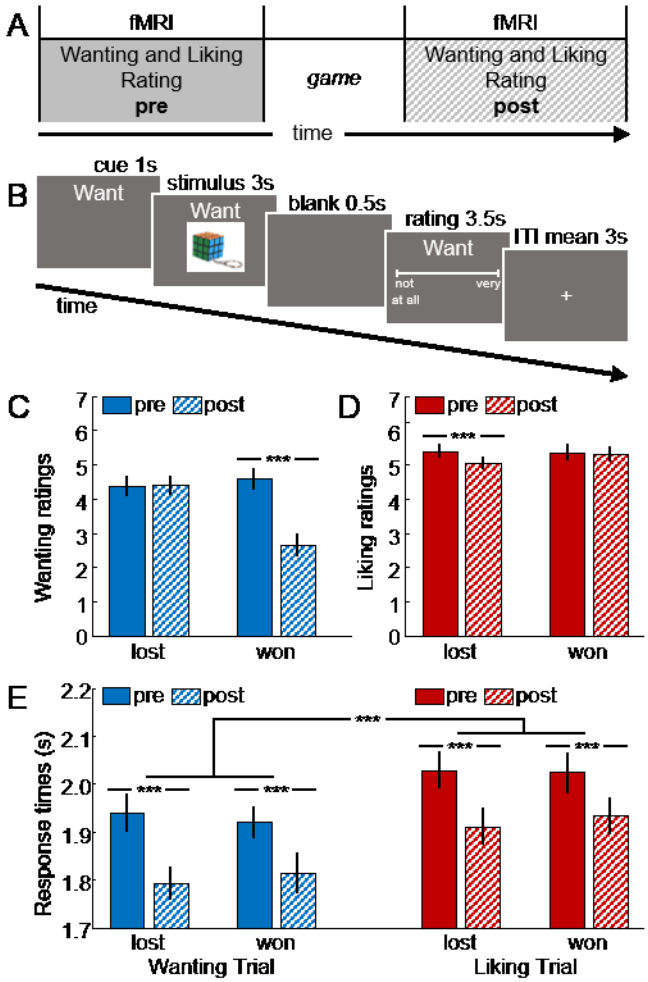

Figure 1. Task and behavior. A. Timeline of the experimental design. Wanting and liking ratings were collected in the scanner. After the initial session (*pre*), participants were removed from the scanner and completed a game on a computer in an adjacent room. Participants were then asked to rate the items in a second session (*post*) in the scanner. **B.** Timing of the scanned task. Wanting and liking judgments, as well as the location of the anchor points of the rating scale, were randomized across trials. **C.** Change in wanting ratings as a function of game outcomes. Wanting decreased from pre to post game specifically for won items but remained similar for lost items (wanting won pre vs. won post: $t(27)=4.81$, $p<0.001$; wanting lost pre vs. lost post: $t(27)=-0.16$, $p=0.873$). **D.** Change in liking ratings as a function of game outcomes. Liking decreased from pre to post game specifically for lost items but remained similar for won items (liking won pre vs. won post: $t(27)=0.52$, $p=0.609$; liking lost pre vs. lost post: $t(27)=4.50$, $p<0.001$). **E.** Response times for the ratings. Participants became significantly faster from pre to post game and took significantly longer to make liking judgments compared to wanting judgments. ***p<.001; error bars depict SEM.

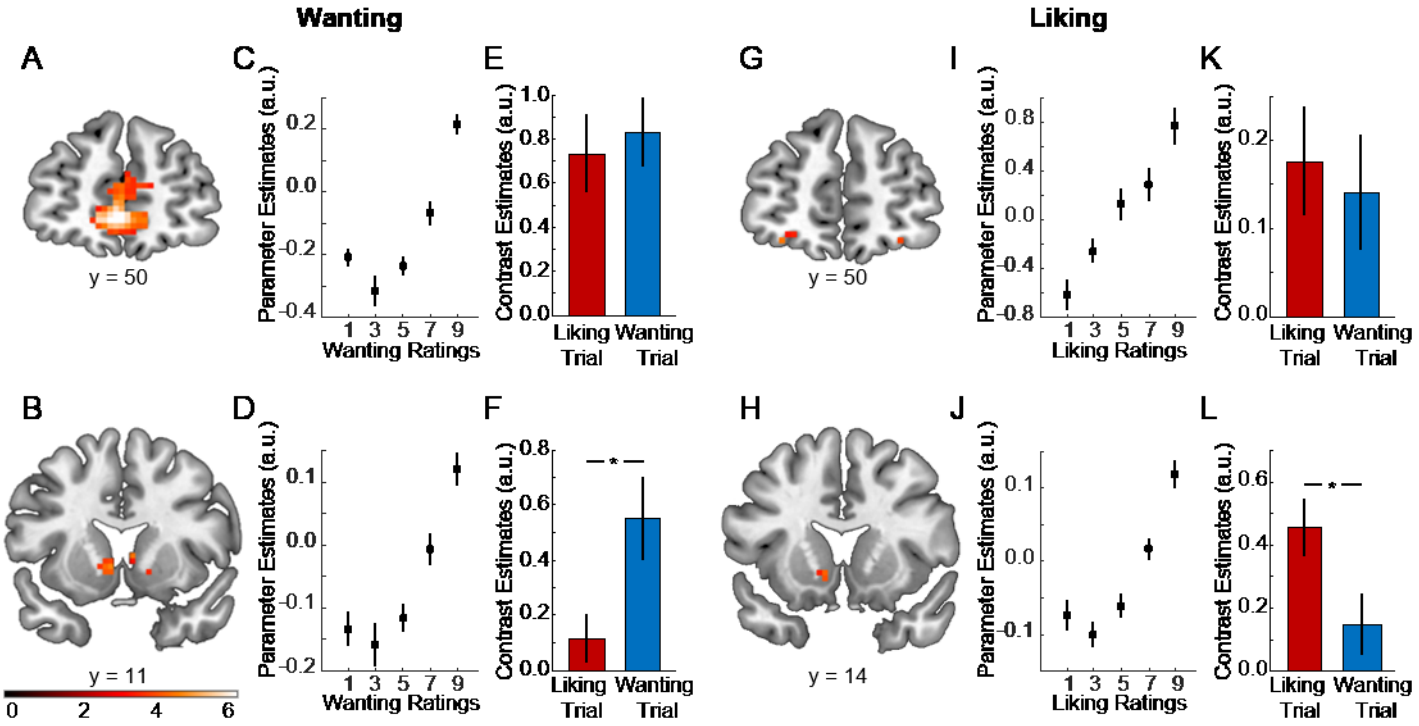

Figure 2. Neural correlates of Wanting and Liking. A-D: Wanting ratings correlated with activity in the mPFC (**A & C**) and VS (**B & D**). **E-F**: Contrast estimates for the wanting parametric modulators during liking and wanting trials. **G-J:** Liking ratings correlated with activity in the OFC (**G & I**) and VS (**H & J**). **K-L:** Contrast estimates for the liking parametric modulators during liking and wanting trials. *p<.05; error bars depict SEM.

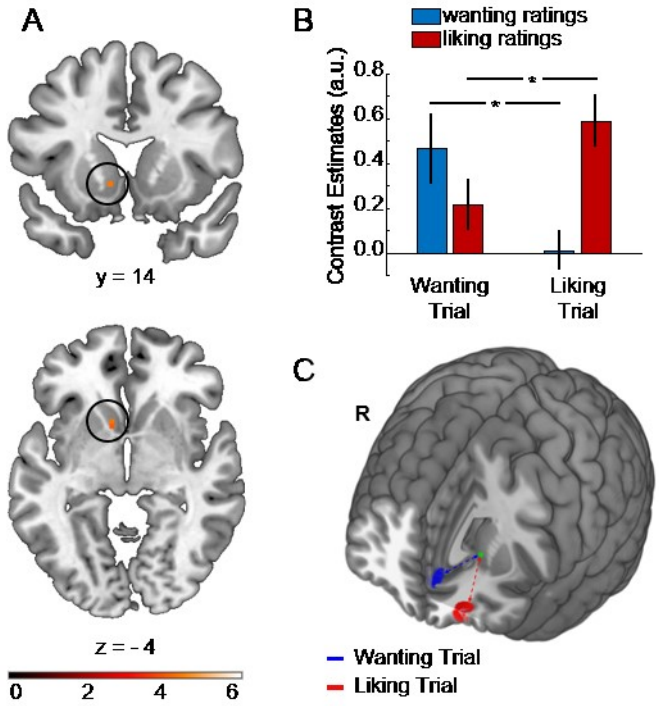

Figure 3. Gating of behaviorally relevant reward dimensions by fronto-striatal connectivity. A-B: Behaviorally relevant coding of wanting or liking levels in the VS. Conjunction of the parametric modulators for wanting and liking (**A**). Activity in the VS encoded wanting ratings during wanting trials and liking ratings during liking trials (**B**). **C.** Functional connectivity between VS and prefrontal activations related to wanting and liking depended on whether participants were making wanting or liking judgments. *p<.05; error bars depict SEM.

Table 1. Brain regions associated with liking or wanting irrespective of judgment type.

		MNI Coordinate				
	Region	*x*	*y*	*z*	*T*	*k* voxels
Liking	OFC	-24	47	-14	6.23*	11
	Posterior cingulate	0	-34	25	6.34*	250
	VS	-9	14	-5	4.41	6
	Pallidum	-15	5	-2	4.69	2
Wanting	Medial OFC	0	50	-5	6.56*	180
	mPFC	-3	44	-2	6.93*	356
	left VS	-6	11	-2	4.83	22
	right VS	6	11	4	4.63	7
		12	14	-11	4.27	3

*Results surviving voxel-wise FWE-correction for multiple comparisons, * indicates p<0.05 corrected for multiple comparisons across the whole brain, all other regions significant after small volume correction, cluster size k based on p<0.001 uncorrected threshold.* MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; VS, Ventral Striatum; mPFC, medial prefrontal cortex.

B. Appendix to Study 2

Dopamine D2-Receptor Blockade Enhances Decoding of Prefrontal Signals in Humans

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Abstract

The prefrontal cortex houses representations critical for ongoing and future behavior expressed in the form of patterns of neural activity. Dopamine has long been suggested to play a key role in the integrity of such representations, with D2-receptor activation rendering them flexible but weak. However, it is currently unknown whether and how D2-receptor activation affects prefrontal representations in humans. In the current study, we use dopamine receptor-specific pharmacology and multivoxel pattern-based functional magnetic resonance imaging to test the hypothesis that blocking D2-receptor activation enhances prefrontal representations. Human subjects performed a simple reward prediction task after double-blind and placebo controlled administration of the D2-receptor antagonist amisulpride. Using a whole-brain searchlight decoding approach we show that D2-receptor blockade enhances decoding of reward signals in the medial orbitofrontal cortex. Examination of activity patterns suggests that amisulpride increases the separation of activity patterns related to reward versus no reward. Moreover, consistent with the cortical distribution of D2 receptors, *post hoc* analyses showed enhanced decoding of motor signals in motor cortex, but not of visual signals in visual cortex. These results suggest that D2-receptor blockade enhances content-specific representations in frontal cortex, presumably by a dopamine-mediated increase in pattern separation. These findings are in line with a dual-state model of prefrontal dopamine, and provide new insights into the potential mechanism of action of dopaminergic drugs.

Introduction

The prefrontal cortex is critical for higher cognitive functions and goal-directed behavior (Goldman-Rakic, 1987; Fuster, 2001; Miller and Cohen, 2001). Specifically, sustained activity of neuronal populations in the prefrontal cortex of animals represents and maintains information for subsequent utilization (Goldman-Rakic, 1996). The fidelity of these representations has been suggested to be modulated by dopamine in a receptor-specific manner (Durstewitz et al., 2000). More specifically, a physiologically plausible dual-state model suggests that D2-receptor activation renders prefrontal representations prone to interference and disruption by allowing for several simultaneous but weak network representations (Durstewitz et al., 2000; Seamans et al., 2001). Accordingly, blockade of D2-receptor activation should, in turn, enhance prefrontal representations by inhibiting potentially interfering concurrent representations (Seamans and Yang, 2004). However, the effects of dopamine D2-receptor blockade on cognitive representations in the human prefrontal cortex have remained elusive.

Here we use dopamine receptor-specific pharmacology and multivoxel pattern-based fMRI to test the hypothesis that D2-receptor blockade enhances prefrontal reward signals in humans. Reward representations are fundamental for goal-directed behavior, learning, and decision-making. A prefrontal area key for representing reward-related information is the orbitofrontal cortex (OFC; Murray et al., 2007; Wallis, 2007; Padoa-Schioppa, 2011), and neurons in this region have been shown to maintain reward information throughout delays (Tremblay and Schultz, 1999; Murray et al., 2007; Lara et al., 2009). Despite anatomical and cytoarchitectural differences in the OFC of different species (Wallis, 2012), neural signatures of reward value have been identified in the OFC of rodents (Schoenbaum et al., 1998; van Duuren et al., 2008; Takahashi et al., 2009), nonhuman primates (Tremblay and Schultz, 1999; Padoa-Schioppa and Assad, 2006; Morrison and Salzman, 2009; Kennerley et al., 2011), and humans (Gottfried et al., 2003; Lebreton et al., 2009; Kahnt et al., 2010; Hare et al., 2011; Wunderlich et al., 2012; Barron et al., 2013; McNamee et al., 2013). Reward signals can be decoded from fMRI activity in the OFC using multivoxel pattern analysis (MVPA) techniques (Kahnt et al., 2010; Vickery et al., 2011; McNamee et al., 2013; Kahnt et al., 2014). Instead of focusing on

single fMRI voxels, MVPA techniques combine the activity of multiple voxels and are thus capable of identifying signals that are encoded in the distributed activity of neuronal populations (Haxby et al., 2001; Haynes and Rees, 2005; Kamitani and Tong, 2005). Here we use this technique to estimate a proxy of the fidelity of prefrontal reward representations. Specifically, we reasoned that enhanced prefrontal representations should be accompanied by increased fMRI pattern separation between reward and no reward, and thus lead to increased decoding accuracy. Using this MVPA measure, we examine the effects of dopamine D2-receptor blockade on the decoding of reward signals in the human OFC. In particular, we hypothesize that blocking D2-receptor activation using the D2/D3-receptor antagonist amisulpride (Rosenzweig et al., 2002) enhances decoding of reward.

Materials and Methods

Subjects

In total, 53 right-handed, male subjects participated in the study. Two subjects (both in the placebo group) failed to follow the instructions and were excluded. This left 51 subjects, aged 18–27 years (22.4 ± 0.28 years mean ± SEM). Before the experiment (1 h 30 min ± 4 min), subjects received a pill containing either placebo (N = 24) or 400 mg of the D2-receptor antagonist amisulpride (N = 27) in a randomized and double-blind fashion. To enhance and equate absorption time across subjects, subjects were asked to fast for 6 h before the experiment. Groups did not differ in age ($t = 0.83$, $p = 0.41$) or weight ($t = 0.36$, $p = 0.72$), and subjects were unaware of whether or not they received the drug, as assessed by postexperimental questionnaires ($\chi^2 = 0.10$, $p = 0.75$).

Task and Stimuli

To investigate neural reward signals we used a noninstrumental outcome prediction task (Kahnt et al., 2014) in which different visual stimuli were deterministically associated either with reward (CHF 0.20) or with no reward (CHF 0.00). In each trial (Fig. 1A), subjects saw one of four visual cues for 0.6 s, followed by a response mapping screen on which they had to indicate the upcoming reward (+, reward; –,

no reward, x, unsure) using the index, middle, or ring finger of their right hand. To control for preparatory and motor-related signals, associations between buttons and responses were randomized across trials (i.e., in different trials, different buttons had to be pressed to indicate +, −, and x). The response mapping screen stayed on for a total of 1.5 s and was followed by the presentation of the outcome (1 s). Trials were separated by a variable intertrial interval (1.9 – 9.9 s, mean 3.5 s). To control for the visual features of the cues and the outcomes, two different sets of cue-outcome pairs were used. With one pair, the outcomes were shown as images of coins and with the other pair as digits (Fig. 1B). This ensured that the decoded signals were related to reward rather than visual features of cues or outcomes (see below, MVPA searchlight decoding). Outcomes were deterministically (100% cue-outcome contingency) predicted by the cues (associations were randomized across subjects), and each cue-outcome pair was presented 10 times in each of the five scanning runs. Before fMRI data acquisition, subjects performed one training session to learn the cue-outcome associations (Fig. 1C).

fMRI Acquisition and Preprocessing

Functional imaging was performed on a Philips Achieva 3 T whole-body scanner equipped with an 8-channel head coil. During each of the five scanning sessions, 140 T2*-weighted whole-brain EPI images (37 transversal slices acquired in ascending order) were acquired with a TR of 2 s. Imaging parameters were as follows: slice thickness, 3 mm; in-plane resolution, 2.75 × 2.75 mm; TE, 30 ms; flip angle, 90°. Preprocessing was performed using SPM8 and consisted of slice-time correction, realignment, and spatial normalization to the standard EPI template of the MNI, resampling to 3 × 3 × 3 mm voxels. Unsmoothed time series data were used for the MVPA analysis, whereas data for the standard univariate GLM analysis were smoothed using a Gaussian Kernel with 8 mm FWHM.

MVPA Searchlight Decoding

To decode reward representations (reward vs no reward) we used linear support vector classification (SVC) in combination with a searchlight approach that allows whole-brain information mapping without potentially biasing voxel selection (Kriegeskorte et al., 2006; Haynes et al., 2007). At the level of single OFC neurons,

reward information is represented either positively (more activation for higher value) or negatively (more activation for lower value; Schoenbaum et al., 1998; Morrison and Salzman, 2009; Kennerley et al., 2011). The two populations are intercalated in the OFC (Morrison and Salzman, 2009), making it difficult to identify these signals using conventional univariate fMRI analyses (Kennerley et al., 2009). However, individual voxels can happen to cover a slightly higher proportion of one or the other population (i.e., sampling bias), which results in a nonzero response of each voxel (Haynes and Rees, 2005; Kamitani and Tong, 2005). The response biases of a set of voxels form a condition-specific multivoxel response pattern, such that the pattern elicited by the reward condition is different from that elicited by the no reward condition. These different patterns can then be classified as belonging to reward or no reward trials using pattern recognition algorithms (Kahnt et al., 2010, 2011b). However, it should be noted that it is not entirely clear how exactly multivoxel patterns translate to the underlying neurophysiology, and several models accounting for the relationship between multivoxel patterns and neural firing have been proposed. Specifically, in addition to the biased sampling model described above, activity patterns have been suggested to reflect complex spatiotemporal dynamics of the vascular system (Kriegeskorte et al., 2010; Shmuel et al., 2010) and large-scale biases (Mannion et al., 2010; Freeman et al., 2011). Regardless of the exact mechanism, MVPA methods have been widely used to decode signals represented differentially in intercalated neural populations (Haxby et al., 2001; Haynes and Rees, 2005; Kamitani and Tong, 2005; Xue et al., 2010; Kahnt et al., 2011a), and are able to disentangle overlapping representations within single brain regions, such as value and salience in parietal cortex (Kahnt et al., 2014) or color and motion direction in early visual cortex (Seymour et al., 2009).

In a first step, we estimated condition-specific response amplitudes for each voxel and scanning run that were later used as input to the SVC. Specifically, for each fMRI scanning run, we estimated a voxelwise GLM. This GLM contained four regressors for the onsets of the four cue-outcome pairs (duration 3.1 s) that were convolved with a canonical hemodynamic response function, as well as six regressors of no interest, which accounted for variance induced by head motion. The voxelwise parameter estimates for the four regressors of interest represent the response amplitudes to each of the four cue-outcome pairs in each of the five

scanning runs. They were subsequently used as input to a subject-wise SVC decoding analysis described below.

The SVC was performed by using the LIBSVM implementation (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) with a linear kernel and a cost parameter of c = 0.1 [using different cost parameters or a different decoding algorithm (Naive Bayes Classifier) produced similar results]. At each voxel, we formed a searchlight in the form of a sphere with a radius of 10 mm surrounding the center voxel. Thus, each searchlight contained ~170 voxels (different searchlight sizes produced similar results). The activity patterns within each searchlight were used to decode information about reward by using the following cross-validation procedure. We trained an SVC model to classify patterns of parameter estimates for reward versus no reward trials from stimulus set I and obtained the cross-validated decoding accuracy by testing the SVC model on parameter estimates for reward versus no reward trials from stimulus set II (Fig. 2A). This procedure was repeated vice versa by training on stimulus set II and testing on stimulus set I. The decoding accuracies for both directions were averaged to obtain a measure of locally distributed reward information that was assigned to the center voxel of the searchlight. This procedure was repeated for every possible center voxel (i.e., searchlight) and resulted in a subject-wise, whole-brain 3D map of decoding accuracy. Importantly, by training and testing the classifier on data from different stimulus sets, we ensured that decoding accuracy is only related to what is common between the two cue-outcome pairs of each set (i.e., reward information) and not related to the visual features of the cues paired with reward and no reward. Moreover, because decoding accuracy was computed based on model predictions in independent test data, and not based on model fits in the training data, this cross-validation procedure is completely insensitive to potential noise fitting (i.e., overfitting) in the training data (Kriegeskorte et al., 2009).

Group Level Analysis

To identify brain regions where decoding accuracy differed between the two groups, the subject-wise decoding accuracy maps were smoothed with a Gaussian Kernel of 6 mm FWHM and entered into voxelwise two-sample t-tests. This generated a voxelwise whole-brain t-map reflecting the statistical significance of the group

differences in decoding accuracy. Except for exploratory analyses, we corrected for multiple comparisons at the cluster-level by applying a whole-brain FWE-corrected threshold of $p_{FWE\text{-}corr} < 0.05$.

Univariate Analysis

To test for changes in the reward-related fMRI signal between groups, we performed a conventional univariate analysis. This analysis was performed on the smoothed time series data. The GLM contained the same regressors (four regressors for the four cue-outcome pairings) and the six movement parameters. Subject-wise linear contrast images were computed for reward minus no reward and entered into voxelwise two-sample t-tests for group analysis.

Results

Behavior

One and a half hours before the experiment, subjects received a pill containing either placebo (N = 24) or 400 mg of the D2-receptor blocker amisulpride (N = 27) in a randomized parallel double-blind design. Previous studies have shown that a single dose of 400 mg of sulpiride (similar to amisulpride) occupies ~30% of D2 receptors in the striatum (Mehta et al., 2008). To reveal reward representations, subjects performed a noninstrumental outcome prediction task (see Materials and Methods) in which visual cues deterministically (100% cue-outcome contingency) predicted reward or no reward. In each trial, subjects saw one cue and were asked to indicate the upcoming outcome on a randomized response mapping screen before the actual outcome was shown (Fig. 1A). Two different pairs of cues predicted reward or no reward either in the form of coins or numbers (Fig. 1B). To make a correct response on a given trial, subjects had to represent the predicted reward and act on this representation.

Subjects in both groups learned the associations between all visual cues and outcomes before the first scanning run and maintained high performance throughout scanning (Fig. 1C). In line with the notion that amisulpride induces very little behavioral effects (Rosenzweig et al., 2002), groups did not differ in any

behavioral learning or performance parameters. Specifically, a time by group ANOVA on the percentage of correct responses revealed a significant effect of time ($F(59,2891) = 23.30$, $p < 0.001$), but no effect of group (amisulpride vs placebo, $F(1,49) = 1.42$, $p = 0.24$), and no group by time interaction ($F(59,2891) = 0.93$, $p = 0.62$). To capture potential differences in learning speed between groups, we estimated the learning rate (α) of a simple reinforcement learning (RL) model (Sutton and Barto, 1998; Kahnt et al., 2009). Mirroring task performance, the individual learning rates did not differ between groups (amisulpride, $\alpha = 0.56$, ± 0.07; placebo, $\alpha = 0.64$, ± 0.06; $t = -0.86$, $p = 0.39$). Testing for reward-specific effects, a group (amisulpride vs placebo) by reward (reward vs no reward) ANOVA on the percentage of correct responses (Fig. 1D) did not reveal a significant main effect of group ($F(1,49) = 1.375$, $p = 0.25$), reward ($F(1,49) = 0.238$, $p = 0.63$), or a group by reward interaction ($F(1,49) = 0.001$, $p = 0.98$). A corresponding ANOVA on response times (RTs) revealed a significant effect of reward ($F(1,49) = 128.10$, $p < 0.001$; faster responding in reward than no reward trials) but no significant effect of group ($F(1,49) = 0.27$, $p = 0.61$), and no group by reward interaction ($F(1,49) = 0.27$, $p = 0.61$). In summary, these results demonstrate that groups were well matched with regard to behavioral performance, and that neural reward signals can, therefore, be compared between groups independent of potentially confounding differences in behavior or learning.

Prefrontal reward signals

We revealed neural reward signals by applying multivoxel pattern-based decoding techniques. Specifically, using a searchlight-decoding approach (Kriegeskorte et al., 2006; Haynes et al., 2007) and linear SVC we searched for information about reward value that is contained in locally distributed multivoxel patterns of fMRI activity (see Materials and Methods). To avoid confounds related to the specific (e.g., visual) features of the cues and to ensure that classifier performance is only driven by reward information, we used a cross-classification procedure. Specifically, we trained the SVC model on the multivoxel response patterns acquired during the presentation of one set of cue-outcome pairs (reward vs no reward), and tested it on the multivoxel response patterns evoked by the other set of cue-outcome pairs (Fig. 2A).

We hypothesized that D2-receptor blockade should reduce the D2-mediated weakening of prefrontal representations (Seamans and Yang, 2004) and thus enhance fMRI pattern separation between reward and no reward trials, which in turn should increase decoding accuracy in the amisulpride group. In line with this prediction, we found significantly ($p_{FWE\text{-}corr} < 0.05$) higher decoding accuracies in the medial OFC (MNI coordinates [x, y, z], [−3, 35, −23], t = 6.07, $p_{FWE\text{-}corr} = 0.012$) in the amisulpride than the placebo group (Fig. 2B, see Table 1 for results at an uncorrected threshold). A similar effect in the left dorsolateral prefrontal cortex did not survive correction for multiple comparisons (left middle and superior frontal gyrus, [−27, 14, 55], t = 4.04, $p_{FWE\text{-}corr} = 0.058$). Exploratory analyses revealed no significant ($p_{uncorr} < 0.001$) voxels when searching for higher decoding accuracy in the placebo than amisulpride group. The same set of results was obtained when behavioral performance was included as covariate of no interest, demonstrating that (nonsignificant) behavioral differences did not affect our decoding results.

The decoding results described above provide only an abstract picture of the changes induced by amisulpride. We further examined the pattern changes in the OFC using more direct and parsimonious methods. Specifically, we tested whether amisulpride enhances pattern separation between reward and no reward trials in the OFC, by computing the mean squared difference between the activity patterns related to reward and no reward trials. Comparing this measure between the two groups demonstrated significantly greater pattern separation in the amisulpride compared with the placebo group (t = 2.29, p = 0.01, one-tailed; Fig. 3). Notably, these changes in pattern separation were not accompanied by changes in the variance of the patterns per se (t = 0.55, p = 0.58). Moreover, we tested whether patterns in the amisulpride group were also more consistent across time by correlating the reward coding patterns from different scanning runs. As expected, this revealed significantly higher temporal pattern consistency in the amisulpride versus the placebo group (t = 1.90, p = 0.03, one-tailed).

We confirmed the results of the searchlight analysis using an independent region of interest analysis in anatomically defined subregions of the OFC (medial, central, and lateral OFC; Fig. 4A). Training and testing the SVC on the activity patterns within these anatomical regions (using the cross-classification procedure described above) revealed enhanced reward representation with D2-receptor

blockade in the medial OFC ($t = 2.67$, $p = 0.01$, one-tailed) but not the central ($t = 1.55$, $p = 0.13$) and lateral OFC ($t = 1.50$, $p = 0.14$, Fig. 4B). Moreover, pattern separation and pattern consistency over time were significantly enhanced in the amisulpride relative to the placebo group in the anatomically defined medial OFC (pattern separation, $t = 2.17$, $p = 0.02$; pattern consistency $t = 2.69$, $p = 0.005$, one-tailed), but not in the central OFC (pattern separation, $t = 1.24$, $p = 0.11$; pattern consistency, $t = 1.31$, $p = 0.10$, one-tailed) or the lateral OFC (pattern separation, $t = 1.21$, $p = 0.11$; pattern consistency, $t = 1.34$, $p = 0.09$, one-tailed).

To examine the effects of amisulpride on mean BOLD signals, we performed a standard univariate analysis (see Materials and Methods). Univariate BOLD signals in the medial OFC did not differ between groups ($t = -0.83$, $p = 0.41$). However, an exploratory voxelwise whole-brain analysis revealed elevated activation in reward > no-reward trials in the amisulpride group compared with the placebo group in the ventral striatum ([15, 14, −11], $t = 3.05$, $p_{uncorr} < 0.005$). Together, these findings suggest that whereas amisulpride may enhance the average reward signal in the ventral striatum, the effects on prefrontal representations are more subtle. Specifically, amisulpride in the prefrontal cortex enhances the decoding of reward information by increasing pattern separation between the reward and no reward trials as well as pattern consistency across time, without changing the mean signal between conditions.

Other cortical signals

An important question is whether the enhancement of decodability by D2-receptor blockade is specific for reward signals. In principle, amisulpride could generally increase decoding of content-specific signals in cortical areas with substantial D2-receptor density. In a set of post hoc analyses, we, therefore, tested whether amisulpride also enhances decoding of other signals required for task performance. For instance, subjects gave their behavioral response using the index, middle, or ring finger (randomized across trials) of their right hand, which should elicit characteristic activity patterns in premotor and motor cortex of the contralateral hemisphere. Given the presence of D2 receptors in motor cortex (Lidow et al., 1989), amisulpride should enhance decoding of these signals. To test this idea, we decoded the specific motor response that subjects made on a given trial using a leave-one-

run-out cross-validation procedure. Specifically, using a searchlight approach we trained and tested a three-class SVC on activity patterns corresponding to the three fingers that were used to make the response. We found significantly higher decoding accuracy in left premotor (BA 6) and primary motor cortex (BA 4, [−51, −10, 43], t = 3.61, $p_{uncorr} < 0.001$) in the amisulpride relative to the placebo group (Fig. 5). This suggests that amisulpride enhanced the separation of finger-specific fMRI response patterns in areas of motor cortex that represent the fingers of the right hand (Meier et al., 2008).

In contrast, signals in regions with few D2 receptors, such as visual cue representations in occipital cortex (Lidow et al., 1989), should not be changed by amisulpride. As a control, we used a searchlight approach to decode visual signals independent of value (leave-one-run-out training and testing on the left-out run for reward and no reward set I versus reward and no reward set II). In line with the idea that the effects of amisulpride on cortical representations are specific to regions with a high density of D2 receptors, we did not find any significant ($p_{uncorr} > 0.01$) increases (amisulpride > placebo) in the accuracy for visual decoding in early visual areas.

Discussion

In the current study, we examined the relationship between dopamine D2 signaling and prefrontal representations in humans. Dopamine has long been suggested to play a fundamental role in prefrontal functions (Miller and Cohen, 2001; Robbins and Arnsten, 2009; D'Ardenne et al., 2012). For instance, dopamine applied to the primate prefrontal cortex enhances the signal-to-noise ratio of pyramidal neurons representing task-relevant stimuli (Jacob et al., 2013). However, effects of dopamine on prefrontal function seem to be receptor specific, as D1- and D2-specific agents differentially affect the activity patterns of prefrontal neurons (Seamans et al., 2001). For instance, a low dose of a D1 agonist applied to the prefrontal cortex sharpens the spatial tuning of task-sensitive neurons in a spatial working memory task (Vijayraghavan et al., 2007), and blocking prefrontal D1 receptors impairs learning of visuomotor associations (Puig and Miller, 2012). In contrast, D2-receptor

antagonists impair cognitive flexibility without altering behavioral performance (Puig and Miller, 2014), or even fail to affect neuronal activity in the prefrontal cortex at all (Sawaguchi et al., 1990). By showing that D2-receptor blockade enhances decoding of reward signals in the human OFC, our study provides evidence for the importance of receptor-specific dopamine action on prefrontal representations in humans.

We found enhanced decoding not only for reward signals in the OFC but also for motor signals in the motor cortex. In contrast, visual signals in occipital areas remained unaltered by amisulpride. Intriguingly, D2-receptor concentration in the primate brain follows an anterior–posterior gradient with the highest concentration in the prefrontal cortex and the lowest concentration in the occipital cortex, with motor cortex falling in between (Lidow et al., 1989). Our results, therefore, suggest that amisulpride enhances decoding of region-specific information in cortical regions with high D2-receptor density, presumably by enhancing the separation of content-specific response patterns. However, further studies are required to explore the range of signals for which decoding is enhanced by amisulpride.

These results are in line with a dual-state model of prefrontal dopamine, which suggests that activation of D2 and D1 receptors has opposing effects on the strength of network representations (Durstewitz et al., 2000; Seamans et al., 2001). According to the model, when D1 activation predominates (D1-dominated state), only very strong inputs are able to access prefrontal circuits and establish dominant network representations therein. This effect of D1-receptor activation is thought to be mediated by persistent NMDA receptor activation and increased GABAergic inhibition. In contrast, predominant D2 activation (D2-dominated state) is accompanied by reduced GABAergic inhibition allowing multiple inputs to simultaneously establish weak and fragile network representations in the prefrontal cortex. Our results provide support for this model in humans by showing that D2-receptor blockade is sufficient to enhance decoding of prefrontal signals. Specifically, by blocking D2 receptors, amisulpride should have decreased the likelihood of D2-dominated states and increased the likelihood of D1-dominated states (Seamans and Yang, 2004). Hypothetically, this could have strengthened prefrontal representations, which in turn resulted in enhanced fMRI pattern separation and thus improved decoding accuracy. While recent findings call for

modifications of this model (Tseng and O'Donnell, 2007), and the proposed mechanism and functional consequences are therefore presently somewhat speculative, the model predicts that D1-receptor antagonists should weaken prefrontal representations relative to placebo. Unfortunately, such agents are currently unavailable for use in humans. It is important to note that this model was originally designed to account for sustained activity in prefrontal cortex, maintaining sensory or mnemonic representations. Nevertheless, similar mechanisms could apply to activity patterns in motor and premotor cortex, maintaining motor representations.

The model described above focuses on how D2-blockade affects prefrontal representations through local effects on D2 receptors (which are located mainly in layer 5), and the regional specificity of our effects is explained most parsimoniously with this local mechanism. However, more indirect routes and mechanisms may fulfill similar functions. For instance, two opposing pathways project from the striatum through the thalamus back to the cortex (Frank et al., 2004). Activity in the direct pathway is thought to facilitate prefrontal representations, whereas activity in the indirect pathway suppresses representations. Interestingly, neurons in the direct and indirect pathway primarily express D1 and D2 receptors, respectively (Aubert et al., 2000). Reduced activation of the indirect versus the direct pathway could, therefore, have affected the spatial distribution of activity and thus prefrontal signals in our data. Moreover, the striatum and the dopaminergic midbrain (but not the OFC) contain D2 autoreceptors and blocking these could have increased the availability of dopamine in the synaptic cleft. Blocking of D2 autoreceptors could, therefore, lead to an overall increase of DA function, and in theory would lead to a greater global occupation of D1 receptors, especially if D2 receptors are concurrently blocked by amisulpride. Finally, blocking D2 receptors could have shifted the tonic/phasic balance toward D1/NMDA-mediated phasic activity (Goto and Grace, 2005) and thus increased separation of patterns coding reward and no reward.

In the current experiment, we used a simple task to ensure that behavioral performance was matched across groups, allowing a straightforward interpretation of the neural effects. In general, however, it would be interesting to test the effects of enhanced cortical representations on behavioral performance. For instance, if D2-

receptor blockade decreases the ability to flexibly switch between prefrontal representations, amisulpride may reduce distractibility at the cost of reduced cognitive flexibility and increased perseveration (Mehta et al., 2004). Future experiments are needed to test the behavioral markers of altered prefrontal representations.

Phasic increases in dopamine are thought to play a major role in motivation, reward processing, and RL (Berridge and Robinson, 1998; Pessiglione et al., 2006; Bromberg-Martin et al., 2010; Schultz, 2013). Specifically, unpredicted rewards and reward-predictive stimuli activate dopamine neurons (Tobler et al., 2005) and concomitant dopamine release in striatum and prefrontal cortex (Hart et al., 2014) could play a role in implementing behavioral functions. For instance, dopamine is thought to signal reward prediction errors that drive RL (Schultz, 2013). Interestingly, whereas previous studies show reduced RL when blocking dopamine receptors using haloperidol (Pessiglione et al., 2006), individually estimated learning rates of an RL model did not differ in our experiment. This is in line with the fact that amisulpride has generally very limited effects on behavior (Rosenzweig et al., 2002) and learning (Eisenegger et al., 2014), and corroborates the notion that many of the reinforcing effects of dopamine arise only when both D1 and D2 receptors are stimulated (Wise, 2006).

Of note, amisulpride is one of the few relatively selective drugs affecting dopaminergic neurotransmission available for human use. However, D3 and 5-HT7 receptors are also modulated by amisulpride. The D3 receptor belongs to the D2-like family of dopaminergic receptors, activation of which inhibits the formation of cAMP. Thus, it is likely that D3-receptor activation also opposes D1-receptor activation (which facilitates cAMP formation), along with comparable effects on the strength of prefrontal representations. In contrast, very little is known about the effects of 5-HT7 receptor activation on cognitive functioning, except for a role in memory formation, sleep, and psychiatric disorders (Gasbarri and Pompili, 2014). In general, however, the neuromodulator serotonin (5-HT) has been suggested to play a role in punishment processing and aversive learning (Cools et al., 2008), and has been hypothesized to act as an opponent to dopamine (Daw et al., 2002). Thus, given the role of 5-HT in aversive processing, we believe it is unlikely that 5-HT7-receptors contributed to the effects of amisulpride observed in the current study.

In summary, here we have shown a link between dopamine and prefrontal signals, supporting a dual-state model of prefrontal dopamine in which the strength of network representations can be enhanced by blocking D2 receptors. Thus, our results link a theory that is derived from nonhuman animal models of dopamine receptor functioning to human prefrontal function. By suggesting a mechanism by which prefrontal representations can be manipulated, our results have important implications for the treatment of cognitive dysfunctions. Specifically, high doses of amisulpride (400–1200 mg/d) are widely used in the management of positive symptoms in schizophrenia (Curran and Perry, 2001), which include disordered thoughts and speech, hallucinations, and delusions. Such symptoms could result from multiple weak cognitive representations, suggesting that the enhancement of cognitive representations may be an important aspect of the therapeutic drug effect. This potential mechanism also has implications for the management of other psychiatric disorders that are characterized by enhanced cognitive flexibility and attentional deficits such as attention deficit hyperactivity disorder.

Acknowledgments

This work was supported by the Swiss National Science Foundation (grants PP00P1_128574, PP00P1_150739, and CRSII3_141965) and the Swiss National Centre of Competence in Research in Affective Sciences. The BCNI is supported by the Medical Research Council and Wellcome Trust. We acknowledge also the Neuroscience Center Zurich and thank M. Wälti and T. Baumgartner for help with data collection.

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Figures and tables

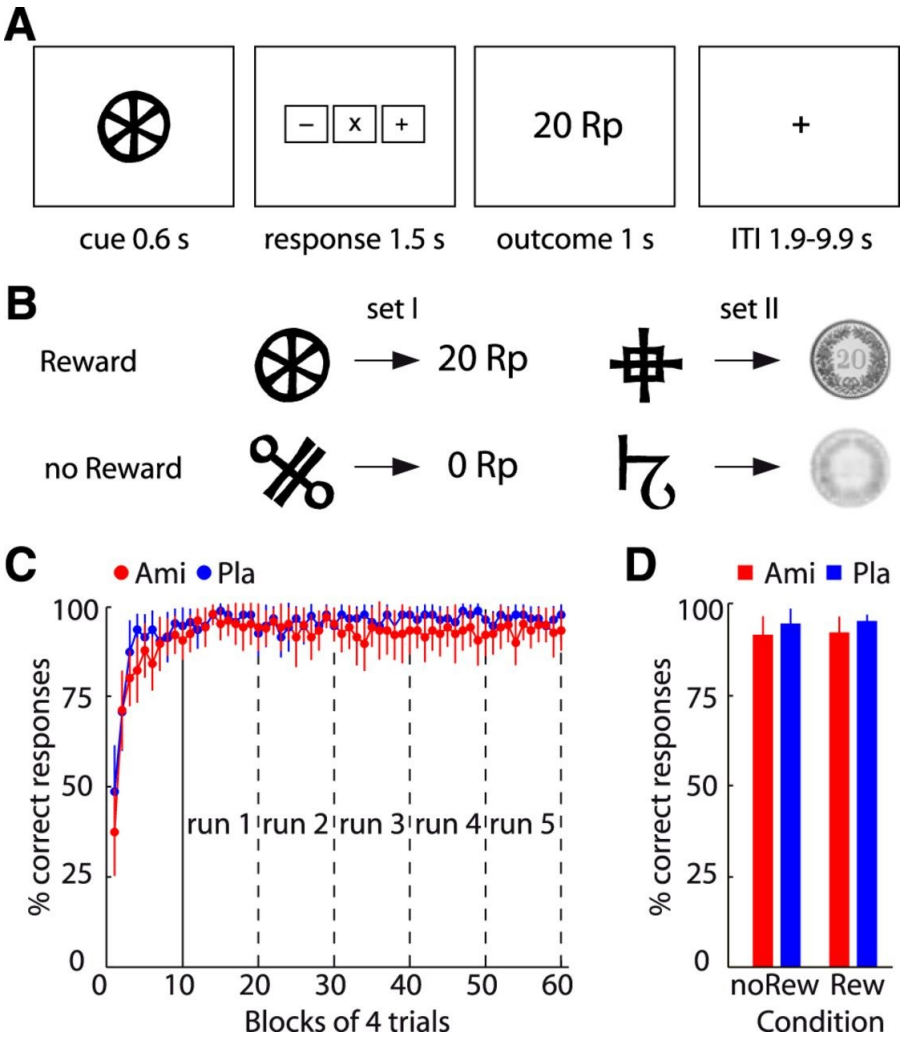

Figure 1. Task and behavioral results. ***A***, Timing of the noninstrumental outcome prediction task. Locations of response options on the response mapping screen were randomized across trials. ***B***, Different cue-outcome pairs were used to control for visual features of cues and outcomes. ***C***, Percentage of correctly predicted outcomes for amisulpride (Ami) and placebo (Pla) group across time (bins of 4 trials each). Because three response options are provided in each trial, chance level is 33%. ***D***, Percentage of correctly predicted no reward (noRew) and reward (Rew) outcomes. Error bars depict 95% CIs.

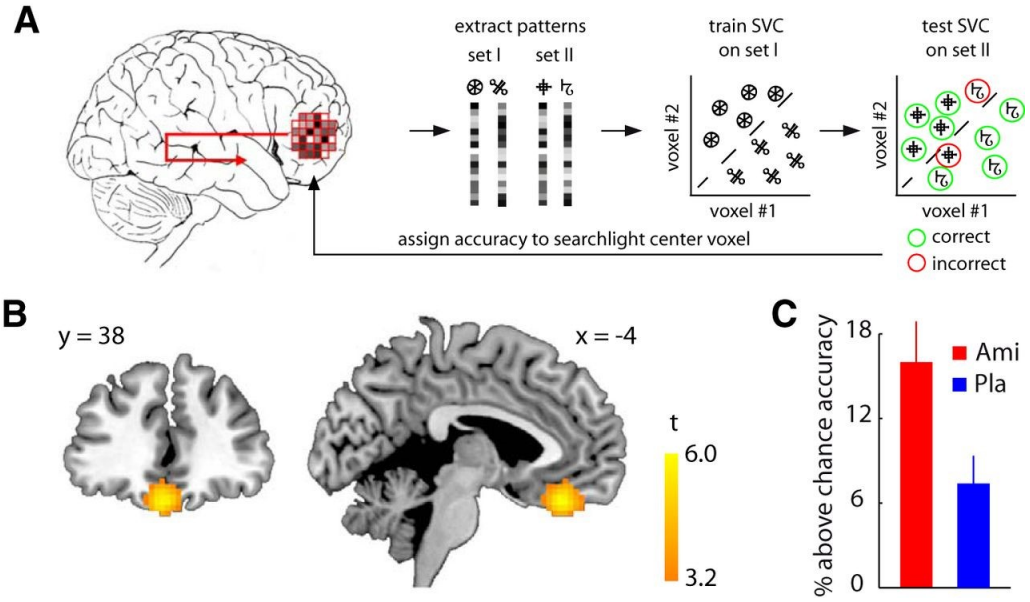

Figure 2. Effects of D2-receptor blockade on reward signals. ***A***, Schematic of the searchlight decoding approach. Activity patterns were extracted for all four cue-outcome pairs from each searchlight. An SVC model was trained to discriminate reward from no reward on set I only or set II only. This yielded predictions that were then tested on the other set (testing on set II after training on set I and vice versa) to obtain decoding accuracy, which was assigned to the center voxel. This procedure was repeated for every searchlight (center voxel) in the entire brain, resulting in a 3D map of decoding accuracy. ***B***, Cluster in the medial OFC with significantly ($p_{FWE\text{-}corr} < 0.05$) higher decoding accuracy in the amisulpride (Ami) than placebo (Pla) group. ***C***, For illustration purposes, bar plots depict averaged decoding accuracy from individual peak searchlights in the OFC cluster for both groups. Error bars depict 95% CI.

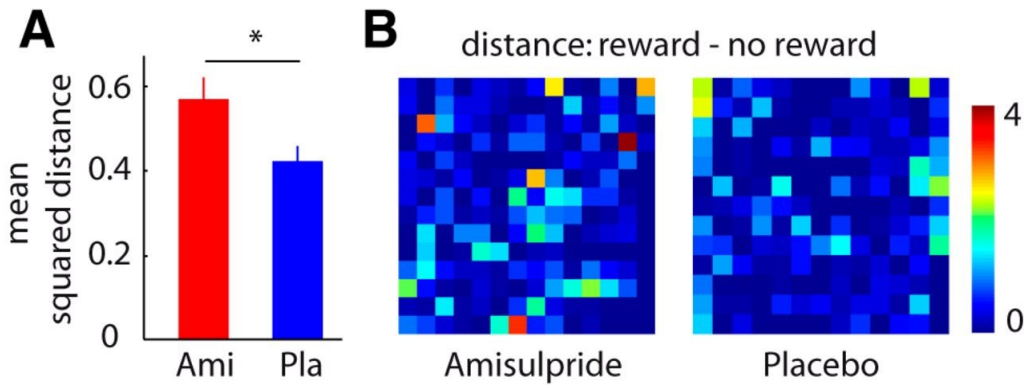

Figure 3. Amisulpride enhances pattern separation in the OFC. ***A***, Bar plots depict average squared difference between activity patterns related to reward and no reward. Asterisk depicts significant two-sample *t* test at $p < 0.05$ (one-tailed). Error bars depict SEM. ***B***, Squared difference between activity patterns related to reward and no reward for a representative subject in the amisulpride group (Ami; left) and in the placebo group (Pla; right). Each pixel represents the squared difference (reward minus no reward) in the activity of one voxel in the medial OFC. The color map represents squared activity difference and is min – max scaled across both displayed patterns. The two subjects were selected such that their average squared pattern difference is close to the mean of their respective group (amisulpride subject = 0.55 [amisulpride group average = 0.57], placebo subject = 0.43 [placebo group average = 0.42]).

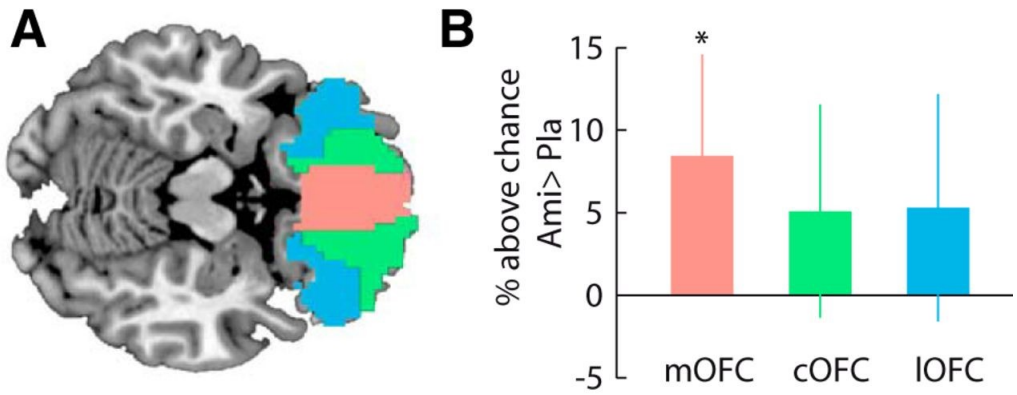

Figure 4. Effects of D2-receptor blockade on reward signals in anatomical ROIs. ***A***, Anatomically defined ROIs in the orbitofrontal cortex derived from the automated anatomical labeling (AAL) atlas. ***B***, Difference in decoding accuracy for reward between groups [amisulpride (Ami) – placebo (Pla)]. Asterisk depicts significant two-sample t tests at $p < 0.05$ (one-tailed). Error bars depict 95% CI. Medial OFC, mOFC; central OFC, cOFC; lateral OFC, lOFC.

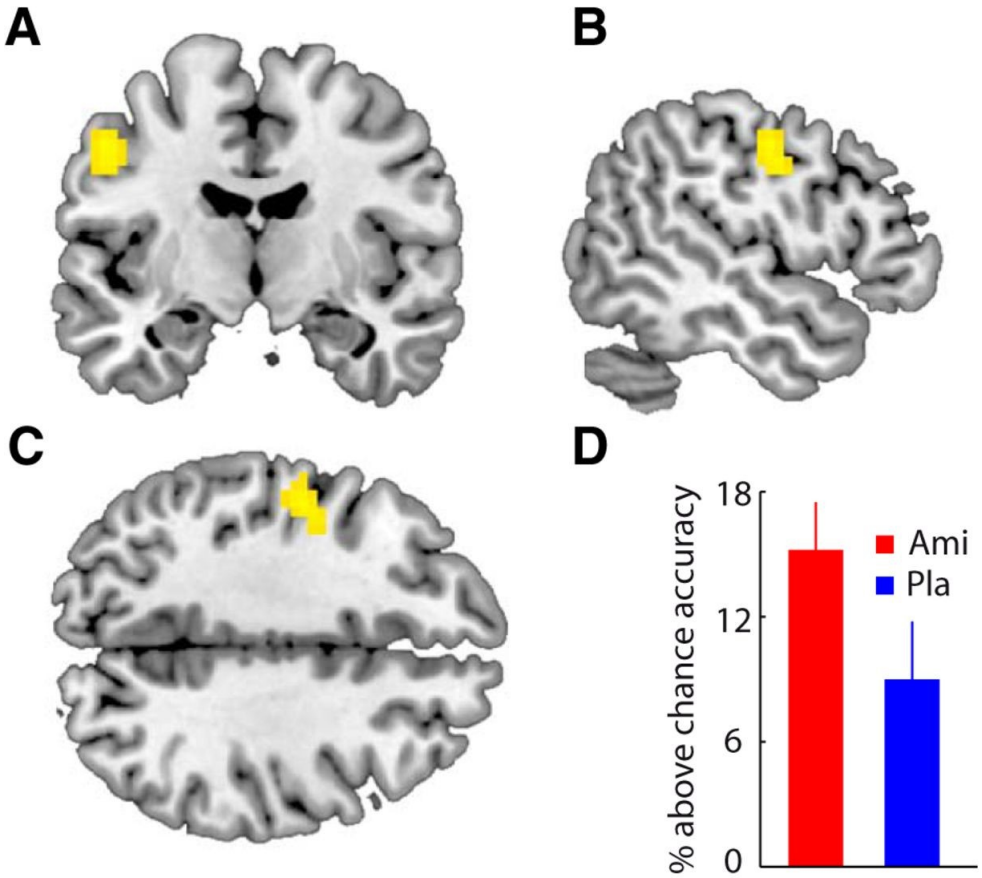

Figure 5. Effects of D2-receptor blockade on motor signals. Coronal (***A***), sagittal (***B***), and transversal (***C***) slices depicting a cluster in motor cortex with significantly higher decoding accuracy for motor response (finger of right hand was used for behavioral response) in the amisulpride (Ami) compared with the placebo (Pla) group. ***D***, For illustration purposes, bar plots depict averaged decoding accuracy from individual peak searchlights in the cluster for both groups. Error bars depict 95% CI.

Table 1. Brain regions with higher decoding accuracy for reward in the amisulpride > placebo group.

Region	MNI Coordinate			*T*	*k* voxels
	x	*y*	*z*		
Medial OFC	−3	35	−23	6,07	186
Left dorsolateral PFC	−27	14	55	4,04	115
Dorsomedial PFC	−6	41	49	3,76	60
Left ventrolateral PFC	−30	50	1	3,74	27
Right inferior TC	54	−43	−8	3,98	40
Left inferior TC	−33	−43	−23	3,95	42

Results thresholded at $p < 0.001$, uncorrected ($k > 15$). TC, temporal cortex.

C. Appendix to Study 3

Dopamine D2/3- and μ-opioid receptor antagonists reduce cue-induced responding and reward impulsivity in humans

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Abstract

Increased responding to drug-associated stimuli (cue reactivity) and an inability to tolerate delayed gratification (reward impulsivity) have been implicated in the development and maintenance of drug addiction. While data from animal studies suggest that both the dopamine and opioid system are involved in these two reward-related processes, their role in humans is less clear. Moreover, dopaminergic and opioidergic drugs have not been directly compared with regard to these functions, even though a deeper understanding of the underlying mechanisms might inform the development of specific treatments for elevated cue reactivity and reward impulsivity. In a randomized, double-blind, between-subject design we administered the selective dopamine D2/D3 receptor antagonist amisulpride (400mg, n=41), the unspecific opioid receptor antagonist naltrexone (50mg, n=40), or placebo (n=40) to healthy humans and measured cue-induced responding with a Pavlovian-instrumental transfer task and reward impulsivity with a delay discounting task. Mood was assessed using a visual analog scale. Compared to placebo, amisulpride significantly suppressed cue-induced responding and reward impulsivity. The effects of naltrexone were similar, although less pronounced. Both amisulpride and naltrexone decreased average mood ratings compared to placebo. Our results demonstrate that a selective blockade of dopamine D2/D3 receptors reduces cue-induced responding and reward impulsivity in healthy humans. Antagonizing μ-opioid receptors has similar effects for cue-induced responding and to a lesser extent for reward impulsivity.

Introduction

Substance addiction is characterized by uncontrolled drug use, drug craving, and a high incidence of relapse even after years of abstinence. Cue reactivity and reward impulsivity are two core features of addiction that play an important role in the development and maintenance of drug addiction as well as relapse (Drummond, 2000). Cue reactivity refers to the ability of drug associated stimuli to increase responding to those drug cues in addiction. It is often used to explain why patients with addiction use drugs and relapse at a higher rate in environments that have been associated with prior drug use. Objects and environments that are paired with drug use become conditioned stimuli capable of independently triggering instrumental drug-seeking behaviors (Drummond, 2000). Not surprisingly, elevated cue-reactivity is consistently found in substance use disorders (Everitt et al., 2001; O'Brien et al., 1998). Reward impulsivity is defined as the inability to delay gratification and wait for a larger reward, in the face of a smaller immediate reward (Hulka et al., 2014). Increased reward impulsivity has been suggested as a stable marker (endophenotype) of addiction (Hulka et al., 2014; Hulka et al., 2015; De Wit, 2009; MacKillop et al., 2011) and may explain the reduced ability of affected individuals to refrain from taking drugs even when continued use is associated with high personal and financial costs.

Since both cue reactivity and reward impulsivity are important factors in drug addiction, understanding their underlying neurochemistry may provide key insights into drug abuse and relapse. Two neurotransmitter systems have been particularly implicated in addiction – the dopamine and the opioid system (Berridge and Robinson, 2011). Opioid receptor agonists and antagonists are commonly prescribed to reduce craving and to prevent relapse in opioid dependence and other forms of substance addiction (Quednow and Herdener, in press). On the other hand, in animal models, most addictive drugs increase dopamine levels in the nucleus accumbens (Di Chiara and Bassareo, 2007) which has been confirmed in humans for stimulant drugs, alcohol, and nicotine (Nutt et al., 2015). Moreover, stimulant-addicted individuals show a blunted dopamine response to acute challenges with stimulants, but increased dopamine release in response to sensory cues associated with drug use (Volkow et al., 2012). It is therefore of high interest to understand

how cue reactivity and reward impulsivity are commonly and differentially influenced by dopamine and opioid blockade.

Here, we investigate the pharmacological basis of cue reactivity and reward impulsivity in healthy volunteers. The use of healthy volunteers to study how reward processing may be altered in addiction offers several important benefits. Firstly, it makes human studies comparable to the numerous animal studies that mainly use pharmacological manipulations on healthy animal subjects. Secondly, using healthy volunteers makes it easier to interpret the results of the pharmacological intervention, since it dissociates drug effects from disorder effects and is not complicated by interactions between drug and disorder. Thirdly, patients with substance use disorders often have comorbidities and are treated with psychotropic medications that potentially interact with experimental drug challenge effects. In the current study, we probe the effect of dopamine and opioid receptor antagonists in a Pavlovian-instrumental transfer (PIT) task and a delay discounting task. PIT is a common measure of cue-induced responding (cue reactivity) that has been used in numerous animal studies and has also been applied to humans (Holmes et al., 2010). It measures the ability of a previously rewarded conditioned stimulus to trigger instrumental responding even in the absence of any rewards. PIT tasks usually employ a three phase design: In an instrumental and a Pavlovian phase, an instrumental response to earn reward is acquired and a Pavlovian conditioned stimulus predicting reward is learned. During the critical test phase, which measures PIT/cue-induced responding, the conditioned stimulus is displayed in the absence of rewards and instrumental responding is recorded. The ability of the conditioned stimulus to elicit instrumental responding during the test phase is considered a model of how drug-associated stimuli can trigger drug seeking behavior (Everitt and Robbins, 2005). Reward impulsivity is often measured using delay discounting tasks (Hulka et al., 2014; Kirby et al., 1999; Kirby and Petry, 2004). In these tasks participants choose between smaller immediate rewards and larger delayed rewards, and reward impulsivity is characterized by an increased preference for smaller immediate rewards over larger delayed rewards i.e. higher discounting (Hulka et al., 2014; Kirby et al., 1999; Kirby and Petry, 2004).

In separate studies, PIT and delay discounting have been linked to the dopamine system (delay discounting: e.g. De Wit et al., 2002; Floresco et al., 2008;

Pine et al., 2010; PIT: e.g. Dickinson et al., 2000; Hebart and Gläscher, 2015; Lex and Hauber, 2008; Ostlund and Maidment, 2012; Wassum et al., 2011) and the opioid system (delay discounting: e.g. Kieres et al., 2004; Love et al., 2009; Pattij et al., 2009; PIT: e.g. Laurent et al., 2012; Peciña and Berridge, 2013). However, the previous results are primarily from animal studies (for a non-exhaustive overview see Table 1) and often contradictory, because various and relatively unselective challenge drugs have been used. Additionally, the rare human studies (Table 1) have mostly tested rather small samples. More importantly, no study directly compared dopaminergic and opioidergic drug challenges on reward impulsivity and cue-induced responding.

To fill this gap, we investigated the role of the dopamine and opioid system in cue-induced responding and reward impulsivity by administering the highly selective D2/D3 receptor antagonist amisulpride, the non-selective opioid antagonist naltrexone and placebo in a randomized, double-blind, between-subject design in healthy volunteers. We used 400 mg amisulpride and 50 mg naltrexone administered orally, a standard dosage with only minor side-effects in several previous studies (Murray et al., 2014; Rosenzweig et al., 2002).

Methods and Materials

Participants

A total of 121 healthy volunteers, recruited from the *Laboratory for Social and Neural Systems Research* subject pool, participated in the study. The sample size was chosen based on previous literature and in order to obtain a statistical power of 80% for detecting significant differences between drug conditions (Rosenzweig et al., 2002). All participants were screened by the recruitment team to ensure they were physically and psychiatrically healthy. Specific exclusion criteria were a history of brain disease or injury, surgery to head or heart, neurological or psychiatric diseases (including alcoholism, depression, schizophrenia, bipolar disorders, claustrophobia, or Parkinson symptoms), a severe medical disease such as diabetes, cancer, insufficiency of liver or kidneys, acute hepatitis, high or low blood pressure, any cardiovascular incidences, epilepsy, pregnancy or breastfeeding, past use of opiates

or other drugs that may interact with amisulpride or naltrexone (such as stimulants). Illegal drug use (amphetamines, barbiturates, buprenorphine, benzodiazepines, cannabis, cocaine, MDMA, methadone, morphine/opiates) was controlled by drug urine testing (M-10/5-DT, Diagnostik Nord, Schwerin, Germany) and cardiac health was confirmed by an electrocardiogram. All participants provided written informed consent. The study was approved by the ethics committee of the Canton of Zurich and registered on www.clinicaltrials.gov (NCT02557984).

Procedure

On average 3h (+/-1.10 min, SEM) before the experimental tasks, participants received a pill containing either placebo (N=40), 400 mg amisulpride (N=41), or 50 mg naltrexone (N=40) in a randomized and double-blind fashion (Figure S1). Randomization was performed in blocks of 9 participants by the study pharmacist. Amisulpride is a selective dopamine D2/D3 receptor antagonist, while naltrexone is an unspecific opioid receptor antagonist which acts primarily on the μ- and κ-opioid receptors, with lesser and more variable effects on δ-opioid receptors (Weerts et al., 2008; Rosenzweig et al., 2002). The two active doses were chosen to result in comparable neurochemical responses. While 400mg amisulpride usually result in ~50-80% D2 receptor occupancy (Vernaleken et al., 2004; Bressan et al., 2004; La Fougère et al., 2005; Meisenzahl et al., 2008), 50mg naltrexone normally cause >90% mu-opioid receptor occupancy (Weerts et al., 2008; Weerts et al., 2013). As D2 receptor occupancies of >90% are only attainable with amisulpride doses of 800mg or higher (Vernaleken et al., 2004; La Fougère et al., 2005; Meisenzahl et al., 2008), we nevertheless decided to compare 400mg amisulpride and 50mg naltrexone – doses which are both well tolerated in healthy subjects (Murray et al., 2014; Rosenzweig et al., 2002) – in order to avoid extrapyramidal side effects potentially associated with higher amisulpride doses. To enhance and equate absorption time across participants, all participants were asked not to eat for 6h before arrival. After task completion, participants answered post experimental questionnaires, which probed whether they thought they had received a drug or placebo and also measured their mood (one rating was not recorded in the placebo group). Using high performance liquid chromatography-mass spectrometry, amisulpride and

naltrexone blood plasma levels immediately before and after the behavioral tasks were determined in order to control for absorption of the drugs (amisulpride before: 618 µg/L, after: 915 µg/L, mean: 767 µg/L; naltrexone before: 2.98 µg/L, after: 2.50 µg/L, mean: 2.74 µg/L). There was no correlation between blood plasma level and task performance (*PIT*: $|r|<0.20$, $p>0.24$, $N_{amisulpride}=35$, $N_{naltrexone}=34$; *DD*: $|r|<0.15$, $p>0.36$, $N_{amisulpride}=40$, $N_{naltrexone}=40$).

Pavlovian-instrumental transfer task

The PIT task (duration: 23.46 min +/-0.42) followed the standard three-phase PIT design (please refer to the supplement for a more detailed description) according to the protocol of Lovibond and Colagiuri (2013). Initially, in the instrumental conditioning phase, participants needed to press a button in order to earn a chocolate M&M reward on a variable-ratio 10 schedule. Subsequently, in the Pavlovian phase, a differential-conditioning procedure was used in which an appetitively conditioned stimulus (CS+) was always paired with the delivery of a chocolate M&M reward, whereas a neutral stimulus (CS-) was always presented with no outcome. Lastly, participants completed the transfer-test phase, where no rewards were available. Both the CS+ and the CS- were presented twice for 10 sec in random order, while button-presses were recorded (Figure S2). Before and after the task, participants were asked to indicate their desire for M&Ms, in order to control for hunger levels. Using the same standard as in the previous study (Lovibond and Colagiuri, 2013), 2 placebo, 6 amisulpride, and 6 naltrexone participants did not meet the criterion of the instrumental phase and were therefore excluded from the PIT analysis. For an overview of excluded subjects for each task, please refer to Table S1.

Delay discounting task

After the PIT task, participants completed the Kirby (1999) Monetary Choice Questionnaire to measure delay discounting (duration: 1.8 min +/-0.04). The questionnaire consisted of 27 hypothetical decisions in which participants chose between a smaller, immediate monetary reward and a larger, delayed monetary reward. It included nine questions for each of three delayed reward magnitudes (small, medium and large). The monetary rewards varied between 11 CHF and 80

CHF for immediate rewards, and between 25 CHF and 85 CHF for delayed rewards. The delays of the delayed reward varied between 7 and 186 days. One female subject in the amisulpride group did not complete the delay discounting task and was therefore excluded from all analyses of this task.

Assessment of affect, mood, and trait impulsivity

Before drug administration participants completed the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) in order to measure trait impulsivity, the short version of the Action Regulating Emotion Systems (ARES) questionnaire (Hartig and Moosbrugger, 2003) to check for differences in the Behavioral Inhibition and the Behavioral Activation System scales (BIS/BAS), as well as the Affect Intensity Measure (AIM; Larsen and Diener, 1987) to assess affective responsiveness.

After the behavioral tasks, participants rated their current mood on the computer using a visual analog scale that ranged from 0 (very bad mood) to 100 (very good mood). They were instructed to "please mark on the scale how you feel right now."

Statistical Analysis

To assess whether our groups differed in age, body mass index (BMI), years of education, trait impulsivity, BIS/BAS score, and affect intensity, we conducted one-way ANOVAs with these measures. Additionally, we performed a Chi-Square analysis of whether the subject correctly guessed if they received a medication or placebo.

In order to assess Pavlovian and instrumental learning, we analyzed the performance of the groups in the first two phases of the PIT task, using one-way ANOVAs with the between-subject factor drug group. Specifically, we compared the number and frequency of button-presses, the time participants took to reach the criterion for the instrumental phase, and the ratings of the reward contingencies for the Pavlovian phase. For the main analysis of interest, we focused on differences in the number of button-presses during the transfer-test phase. We normalized the button-presses during the CS test phase by the number of responses during the initial extinction period of the transfer-test phase. However, the results did not change when the raw (non-normalized) data was used and the groups did not differ

significantly in button-pressing during the extinction period (Table S2). In order to probe the cue-related increase in instrumental responding, we compared button-presses during the 10 sec CS presentation with the button-presses in the 10 sec before the CS presentation for CS+ versus CS-. We performed a mixed-model ANOVA to compare the two drug groups with the placebo group, with group as the between subject factor and CS-type and time as the within subject factors. Significant findings ($p<.05$) were followed by post hoc t-test analyses.

For the delay discounting task, we measured how often participants chose the smaller immediate reward, as opposed to the larger delayed reward to estimate reward discounting. More frequent choice of immediate rewards corresponds to stronger discounting. This use of the proportion of immediate rewards chosen allowed us to analyze the discounting behavior without relying on assumptions about the shape of the discounting curve for the individual participants (Myerson et al., 2014). However, using Kirby's estimation to determine the k values of the individuals (Kirby et al., 1999) or using logistic regression (Wileyto et al., 2004) did not change the pattern of results (Table S3). The proportion of immediate rewards chosen for each of the three groups was contrasted using a one-way ANOVA for all rewards, as well as a repeated-measures ANOVA to include the within subject factor reward magnitude. As with the PIT task, significant findings ($p<.05$) were followed by post hoc t-test analyses.

Additionally, using Pearson correlations we investigated how closely related the behaviors of the participants in the two tasks were and, in an exploratory analysis, how mood was related to the performance in the tasks.

Results

The three groups did not differ in age, BMI, years of education, trait impulsivity, BIS/BAS scores, and affect intensity (one-way ANOVAs, all $F(2,118)<1.86$, $p>0.16$; Table S4). Furthermore, participants were unaware whether they received one of the drugs or placebo, as assessed by post experimental questionnaires ($\chi^2(1)=1.00$, $p=.32$).

PIT

To assess cue-induced responding, we compared the number of button-presses during the transfer test phase. Contrasting CS-induced button-presses against pre-CS responding revealed a significant effect of time ($F(1,104)=5.99$, $p<.05$). There was also a significant main effect of CS type, with the rewarded CS increasing button-presses in contrast to the unrewarded CS ($F(1,104)=18.54$, $p<.0001$). Moreover, in line with a transfer effect, CS type interacted with time ($F(1,104)=11.17$, $p<.001$), that is button-presses increased specifically during the CS+ presentation. Importantly, we found a group*CS type*time interaction ($F(2,104)=3.75$, $p<.05$), indicating that there were differences between our drug and placebo groups. As can be seen in Figure 1, in the placebo group button-presses increased during the CS+ presentation as opposed to the ten seconds prior to the CS presentation. Both drug groups showed less of an increase in button-pressing during the CS+ than the placebo group (Figure 1d-f). Post-hoc t-tests revealed that for the placebo group the difference between button-pressing during the CS+ presentation was significantly higher than pre CS+ presentation ($t(37)=3.68$, $p<.005$), as well as significantly higher than during the CS- presentation ($t(37)=5.35$, $p<.001$). This was not the case for the amisulpride and naltrexone groups (amisulpride: pre CS+ vs. CS+: $t(34)=0.62$, $p=0.54$; CS+ vs. CS-: $t(34)=1.66$, $p=0.11$; naltrexone: pre CS+ vs. CS+: $t(33)=1.92$, $p=0.06$; CS+ vs. CS-: $t(33)=2.03$, $p=0.05$). Furthermore, in both drug groups, the difference between button-pressing for the rewarded and unrewarded CSs during CS presentation was significantly reduced compared to the placebo group (amisulpride vs. placebo: $t(71)=3.01$, $p<.01$; naltrexone vs. placebo: $t(70)=2.13$, $p<.05$). There was no significant difference between the two drug groups (amisulpride vs. naltrexone: $t(67)=0.60$, $p=.55$). Thus, cue-induced responding was reduced by both amisulpride and naltrexone.

To assess whether the groups differed in how much they desired M&M's before or after the PIT task and in order to rule this out as a potential confound for subsequent analyses, we performed a repeated-measures ANOVA, which indicated that there was no significant main effect of group ($F(2,104)=0.20$, $p=.82$). Thus, the drugs did not impact desire for chocolate as such. Although the mean desire for chocolate across groups decreased from 83.9 (pre-test) to 67.3 (post-test), in all three groups it remained significantly larger than 50, the midpoint of the scale

(placebo: t(37)=4.68, p<.001; amisulpride: t(34)=3.10, p<.01; naltrexone: t(33)=2.98, p<.01).

In order to test whether the groups differed in their performance during the instrumental or Pavlovian phases, we also compared their responding and learning during these phases (Table S2). Participants took on average 2.5 min (+/-0.22 SEM) to complete the instrumental training and performed 113 (+/-0.86) button-presses, or 1.33 (+/-0.08) button-presses per second. There were no significant differences in the number of button-presses (F(2,104)=0.85, p=.43), the frequency of button-presses (F(2,104)=0.08, p=.92), or the time until criterion (F(2,104)=0.41, p=.66). Similarly, in the Pavlovian acquisition phase, there were no differences between the groups in how well they learned the Pavlovian contingencies of the task (F(2,104)=2.08, p=.13). Overall, it seems that while the three groups did not differ in their desire for chocolate or their performance during the instrumental and Pavlovian acquisition phase, they differed in their behavior during the transfer-test phase. Thus, while learning and desire were unaffected by the pharmacological manipulation, cue-induced responding was reduced.

Delay Discounting

To test whether the dopamine and opioid receptor ligands affected reward impulsivity, we compared the performance of the three groups during the delay discounting task. The groups differed significantly in the proportion of immediate rewards chosen (F(2,117)=3.18, p<.05; Figure 2a). Post-hoc t-tests revealed that the amisulpride group chose the smaller immediate rewards significantly less often than the placebo group (t(78)=2.58, p<.01). The difference between the naltrexone and the placebo group did not reach significance (t(78)=1.70, p=.09). These data were largely the same when reward magnitude was included as an additional factor in the analysis. Again, we found a main effect of group (F(2,117)=3.18, p<.05), but also a main effect of reward magnitude (F(2,116)=91.03, p<.0001; Figure 2b), as well as a significant reward magnitude*group interaction (F(4,234)=2.44, p<.05). T-tests indicated that the amisulpride group chose a lower proportion of immediate rewards than the placebo group for all reward magnitudes (small rewards: t(78)=2.02, p<.05; medium rewards: t(78)=2.32, p<.05; large rewards: t(78)=3.17, p<.01). In contrast, although none of the comparisons reached significance, the

difference between naltrexone and placebo participants was highest for small and medium rewards (small rewards: t(78)=1.65, p=.102; medium rewards: t(78)=1.84, p=.07; large rewards: t(78)=1.43, p=.16). There were no significant differences between the two drug groups. Overall, it seems that both pharmacological manipulations led to a reduction in discounting, with the strongest effects for the amisulpride challenge and a non-significant trend for the naltrexone challenge.

Relation between tasks

Although the drugs elicited similar effects on both tasks, there was no significant correlation between the PIT effect and the proportion of immediate rewards chosen (r=0.15, p=.14, N=106; Figure 3). Thus, the two tasks seem to measure different aspects of reward-guided behavior.

Mood

Finally, in an exploratory analysis, we tested if individual differences in mood might have influenced cue-induced responding and reward impulsivity. A one-way ANOVA revealed that the three groups differed in mood ($F(2,116)=3.44$, $p<.05$). The mood of the amisulpride group was not significantly different from the mood of the naltrexone group ($t(78)=0.56$, $p=.58$), but both drug groups showed lower mood ratings than the placebo group (placebo: 67.59 (+/-2.80 SEM); amisulpride: 58.96 (+/-3.00 SEM); naltrexone: 56.30 (+/-3.63 SEM); amisulpride: $t(77)=0.21$, $p<.05$; naltrexone: $t(77)=0.25$, $p<.05$). We, therefore, re-performed all main analyses of group differences in cue-induced responding and reward impulsivity as ANCOVAs, using mood as a covariate, which produced similar results. In an exploratory correlation analysis, we also investigated the influence of mood on our two behavioral tasks. There were no significant correlations between mood and behavioral outcomes in the PIT task, however, the impact of mood on delay discounting differed between the three groups. While there was no correlation in the placebo group, elevated mood went along with a greater number of immediate rewards chosen in the amisulpride group (Figure S3). In contrast, this relationship was reversed for the naltrexone group, where mood correlated negatively with the proportion of immediate rewards chosen. For statistics, please refer to the supplementary results.

Discussion

To our knowledge, this is the first study to contrast the effect of dopamine and opioid receptor blockade on PIT and delay discounting in healthy volunteers. Our data confirm the critical role of dopamine in *both cue-induced responding and reward impulsivity* in humans by showing that dopamine D2/D3 receptor blockade with amisulpride reduced the motivation to obtain immediate rewards in both a Pavlovian-instrumental transfer task and a delay discounting task. A blockade of μ- and κ-opioid receptors with naltrexone had similar albeit less pronounced effects on cue-induced responding, as well as a non-significant trend reduction in reward impulsivity. While both substances reduced mood, they differently affected the relation between mood and delay discounting. Under amisulpride, increased reward impulsivity was correlated with positive mood whereas in the naltrexone group it was associated with negative mood, suggesting that mood might be an important modulator of relapse risk under addiction treatment with dopamine and opioid antagonists.

Cue-induced responding

We found that amisulpride reduced cue-induced responding as measured by PIT. These results concur with animal studies showing that an inactivation of the ventral tegmental area (VTA), which likely decreased dopaminergic activity in the nucleus accumbens, reduced PIT (Corbit et al., 2007; Murschall and Hauber, 2006). Moreover, systemic administration and microinjections in the nucleus accumbens of dopamine receptors antagonists impair the general form of PIT (Dickinson et al., 2000; Lex and Hauber, 2008), whereas intra-accumbal microinjections of the indirect dopamine agonist amphetamine facilitate general PIT (Peciña et al., 2006; Wyvell and Berridge, 2000). Only a single human study has recently investigated the effects of a manipulation of the dopamine system on PIT: Hebart and Gläscher (2015) reported that a dietary depletion of the dopamine precursors tyrosine and phenylalanine reduces appetitive PIT, which is in line with our results. However, depletion of tyrosine/phenylalanine not only decreases dopamine but also noradrenaline synthesis (Booij et al., 2003) and therefore the challenge has less

specific effects on the dopamine system compared to the selective dopamine D2/D3 receptor antagonist amisulpride used in the present study.

The μ- and κ-opioid receptor antagonist naltrexone decreased PIT as well. This finding is in accordance with the report that both a stimulation of dopamine release by amphetamine as well as a stimulation of μ-opioid receptors by DAMGO microinjection in the nucleus accumbens increased cue-triggered levels of motivation to pursue sucrose reward in the PIT (Peciña and Berridge, 2013). Moreover, μ-opioid receptor knock-out mice showed normal PIT while δ-opioid receptor knock-out mice were impaired. Similar effects were observed when μ- or δ-opioid receptor antagonists were injected into the nucleus accumbens (Laurent et al., 2012). One human study has investigated opioid effects on cue reactivity in non-treatment seeking alcoholics (Myrick et al., 2008). The same dosage of naltrexone as used in the current study, over a 7-day period, produced no changes in craving, but led to a reduction in alcohol cue induced neural activation in the ventral striatum. Our findings extend these results to healthy participants, separate the drug effect from the disorder effect, and thereby provide a clearer picture of opioid effects on cue-induced responding.

Reward impulsivity

Our finding of reduced reward impulsivity under amisulpride is in line with previous animal studies showing that the indirect dopamine agonists amphetamine (Evenden and Ryan, 1996; Helms et al., 2006) and cocaine (Logue et al., 1992) increase reward impulsivity, although also contradictory results exist (Wade et al., 2000). Moreover, one small human study (n=13) has also revealed increased reward impulsivity with indirect catecholamine agonism by L-DOPA (Pine et al., 2010; but see De Wit et al., 2002 for opposing results with amphetamine, as well as Hamidovic et al., 2008 for null effects using oramipexole), but found no effect with the unselective dopamine antagonist haloperidol. Our results add to this literature by showing that selective blockade of D2/D3 receptors can reduce reward impulsivity.

Reward impulsivity was moderately reduced by naltrexone, although the reduction did not reach significance. Only few studies have investigated the effects of opioid challenges on reward impulsivity in humans and animals. For example, in one animal study, the μ-opioid receptor agonist morphine dose-dependently

increased reward impulsivity, while naltrexone alone did not affect the value of delayed rewards but blocked the effects of morphine (Kieres et al., 2004). Two very small human studies showed no significant effects of naltrexone on reward impulsivity (9 abstinent alcoholics and 9 healthy controls (Mitchell et al., 2007); 9 abstinent alcoholics and 10 healthy controls (Boettiger et al., 2009)). Interestingly, a PET study using a μ-opioid receptor selective radiotracer revealed that individuals with high trait impulsivity showed elevated density of μ-opioid receptors in regions underpinning reward impulsivity, such as the nucleus accumbens and the amygdala (Love et al., 2009).

It is important to note that the primary effects of amisulpride and naltrexone on reward impulsivity, cue-induced responding, and even mood were relatively similar. This is in line with the recently reported common involvement of the dopamine and the opioid system in the direct control of drug "*wanting*" behavior (Peciña and Berridge, 2013). On the other hand, naltrexone has been shown to block dopamine release in the nucleus accumbens, induced e.g., by alcohol (Benjamin et al., 1993) or feeding (Taber et al., 1998). Indeed, the mesolimbic opioid and dopamine systems appear to be closely linked. For example, opiates inhibit GABAergic interneurons in the midbrain and thereby disinhibit dopamine neurons (Chartoff and Connery, 2014; Lüscher and Malenka, 2011). Consequently, naltrexone may have influenced behavior indirectly by a modulation of accumbal dopamine release. Invasive methods would be required to completely disentangle the direct from the dopamine-mediated impact of opioid receptor stimulation and blockade on reward impulsivity. However, the observation that the two drug challenges differentially affected the relation between mood and reward impulsivity is more in line with independent actions of naltrexone rather than actions that are mediated through an effect on dopamine neurons.

Mood effects

On average, the mood of the amisulpride and of the naltrexone group was lower than the mood of the placebo group. This effect is plausible for naltrexone, for which dysphoria has been reported as a common side-effect (Crowley et al., 1985), however, the negative mood effect of amisulpride is surprising given that the

compound has been shown to be an effective antidepressant (Montgomery, 2002). While these differences could not account for our findings when we included mood as a covariate, it is worth noting that more positive mood has previously been associated with increased reward impulsivity (Cyders et al., 2007). Conversely, anhedonia is associated with reduced reward impulsivity (Lempert and Pizzagalli, 2010) and reduced willingness to exert effort for reward (Hartmann et al., 2015). More importantly, we found that both drug challenges exerted opposite effects on the relation between mood and reward impulsivity but had no effects on the relation between mood and cue-induced responding. This finding, together with the absence of a relation between cue-induced responding and reward impulsivity across the total study sample (Figure 3), suggests that cue reactivity and reward impulsivity may reflect distinct reward processes (see also supplementary discussion). It is conceivable that cue-induced responding is more strongly related to stimulus-induced value prediction whereas reward impulsivity may reflect a bias of immediate rewards on the computation of decision value.

Limitations

The following limitations should be kept in mind when considering our study. 1) Given that the PIT task cannot reasonably be repeated within an individual, we employed a between-subject design, although a within-subject design would have been advantageous regarding the reliability of the results. However, we aimed to compensate this limitation by investigating relatively large samples. 2) In order to maximize the number of subjects in each group, we only tested single doses of the two blockers. Varying the dosage may provide information about the relative influence of the dopamine and opioid system on cue-induced responding and reward impulsivity. 3) Amisulpride blocks not only dopamine D2/3 receptors but also 5-HT7 receptors (Abbas et al., 2009). In this regard it is worth noting that acute serotonin (tryptophan) depletion reduces reactivity to aversive cues, but has no effects on appetitive cues in general versions of PIT (Geurts et al., 2013), which together with our results is in line with the notion that the dopamine and the serotonin systems play opposing roles in appetitive and aversive value processing. 4) The version of our PIT task does not allow to distinguish general forms of cue-induced responding from outcome-specific forms (Burke et al., 2007; Lewis et al.,

2013). This permits only limited comparisons to animal studies that differentiate between these two types of PIT. 5) Our measure of mood as a single item question at the end of the study provides only a global measure of mood state. Future studies should, therefore, apply a more sensitive measure of mood and measure baseline mood, in order to confirm the relationship between mood and reward impulsivity and the modulatory effects of naltrexone.

Conclusions

Although animal research provided promising findings (Parish et al., 2005), the efficacy of dopamine receptor antagonists for the treatment of addiction in humans appears to be limited (Quednow and Herdener, in press). Our data suggest that it may be worth exploring the usefulness of the more specific D2/D3 dopamine receptor antagonist amisulpride, particularly in patients with increased reactivity to drug cues and elevated reward impulsivity. Moreover, it could be of interest to further explore the relationship of mood and reward impulsivity under naltrexone and amisulpride, as the individual mood of the patient could potentially prove to be a relevant factor when deciding between treatment with amisulpride or naltrexone. In conclusion, we show that the opioid system contributes to increased responding to reward cues, while the effects on delay discounting were less pronounced in our study. In contrast, the dopamine system was involved in both responding to reward associated cues and in delay discounting.

Acknowledgements

We thank Tony Dickinson, Lea M. Hulka, and Matthias Liechti for helpful discussions and Peter Bierbaum, Sabine Kern, Patrick Kellner, Mattia Müller, Martin Schläpfer, and Karl Treiber for professional help with data collection.
The study was supported by the Swiss National Science Foundation (PNT: PP00P1_128574, PP00P1_150739; BBQ: PP00P1_123516, and PP00P1_146326).

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Figures and tables

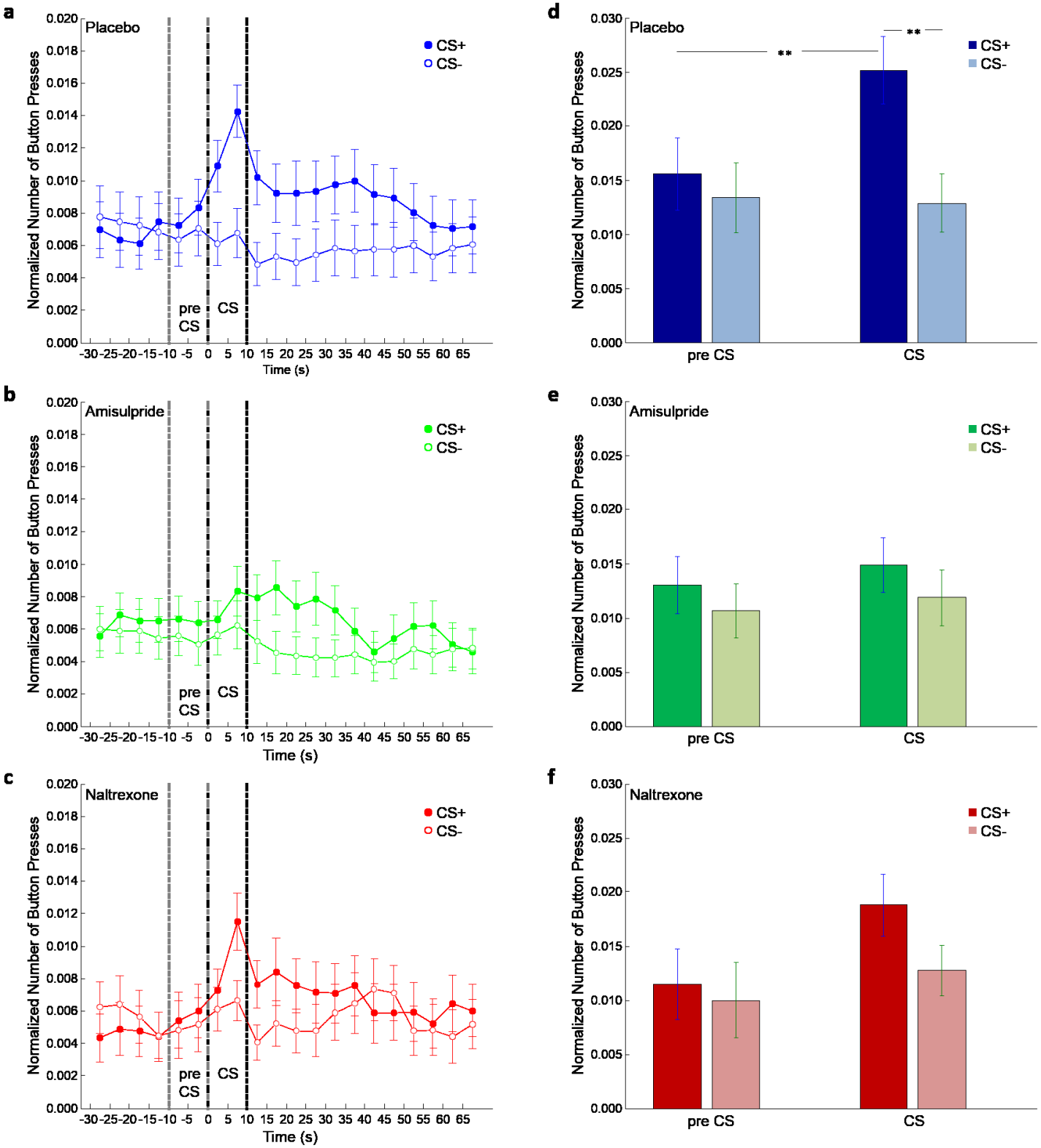

Figure 1. Button-presses during the transfer-test phase of the Pavlovian-instrumental transfer task. a-b: Button-presses in 5-s bins before, during, and after presentation of the conditioned stimuli (CSs) for participants in the **(a)** placebo, **(b)** amisulpride and **(c)** naltrexone groups. The CS+ had previously been paired with chocolate; the CS- had not been paired with chocolate. The dotted lines indicate the pre-CS phase (-10 to 0 s) and the onset and offset of the CS phase (0 to 10 s). **d-f:** Mean number of button-presses in the pre CS phase and the CS phase for participants in the **(d)** placebo, **(e)** amisulpride and **(f)** naltrexone groups (**p<.005). The CS+ is displayed in dark, the CS- in light colors. Error bars represent standard errors of the mean.

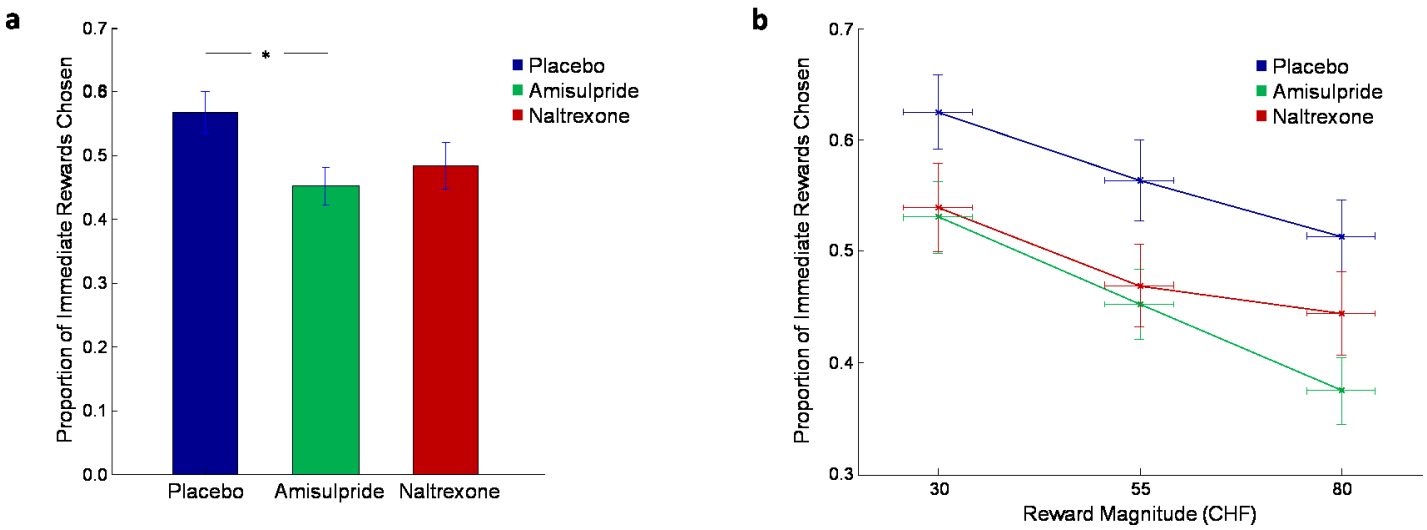

Figure 2. Proportion of smaller immediate rewards chosen in the delay discounting task. (a) Participants in the amisulpride group chose significantly fewer smaller immediate rewards than those in the placebo group (*p<.05). **(b)** Choice behavior of the different groups split by high, medium and large reward magnitudes. Vertical error bars represent standard errors of the mean proportion of immediate rewards chosen; horizontal error bars represent standard errors of the mean reward magnitudes. Higher values indicate higher reward impulsivity.

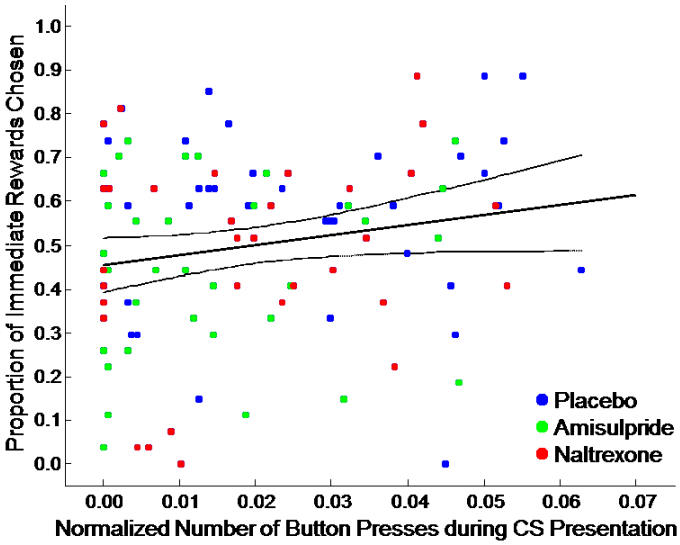

Figure 3. Absence of correlation between performance in the delay discounting task and the Pavlovian-instrumental transfer task. Participants who choose more immediate rewards did not show a proportionate increase in button-pressing during the rewarded conditioned stimulus presentation (r=0.15, p=.14, N=106). Placebo participants are displayed in blue, amisulpride participants in green and naltrexone participants in red.

Table 1. Human and selected animal studies investigating the role of dopamine and opioid in cue-induced responding and reward impulsivity.

		Substance	Dosage	N	Effect	Reference
CUE-INDUCED RESPONDING						
	Dopamine					
Animal						
	D2/3 antagonist	Pimozide	0.25 mg kg^{-1} i.p.	32(B)	↓	20
		α-Flupenthixol	0.5 mg kg^{-1} i.p.	32(B)	↓	20
		Flupenthixol	0.5 mg kg^{-1} i.p.	24	↓	23
		Flupenthixol	0.05 and 0.25 mg kg^{-1} i.p.	14	↓(0.25 mg kg^{-1}) ↔(0.05 mg kg^{-1})	23
		Flupenthixol	0.5 mg kg^{-1} i.p.	16	↓	24
		Raclopride	0.5- and 1.0 μg Intra-NAC	57(B)	↓	22
	D1 antagonist	SCH-23390	0.5- and 0.75 μg Intra-NAC	56(B)	↓	22
	Indirect DA agonist	Amphetamine	20 μg per 0.2 μl intra-NAC	45	↑	29
		Amphetamine	20 μg per 0.2 μl intra-NAC	14	↑	30
		Amphetamine	0.0, 2.0, 10.0 or 20.0 μg per 0.5 μl Intra-NAC	30	↑	31
Human						
	DA/NA depletion	Amino-acid mixture lacking TYR/PHE	90 g	69(B)	↓	21
	Opioid					
Animal						
	Mu-opioid receptor antagonist	CTAP	2 μg μl^{-1} Intra-NAC	48	↔	28
	Delta-opioid receptor antagonist	Naltrindole	5 μg μl^{-1} Intra-NAC	48	↓(For NAc shell) ↔(for Nac core)	28
	Mu-opioid receptor agonist	DAMGO	0.5 μg per 0.2 μl Intra-NAC	55	↑	29
Human						
	Unspecific opioid receptor antagonist	Naltrexone	50 mg p.o.	23(B)	↔(Craving) ↓(fMRI)	32
REWARD IMPULSIVITY						
	Dopamine					
Animal						
	D2/3 antagonist	Flupenthixol	0.5 mg kg^{-1} i.p.	8	↑	18
		Flupenthixol	25, 50 and 100 μg kg^{-1} i.p.	17	↓	33
		Haloperidol	0.01–0.1 mg kg^{-1} i.p.	24	↔	34
		Raclopride	40, 80 and 120 μg kg^{-1} i.p.	17	↓	33
	D1 antagonist	SCH-23390	5, 10 and 20 μg kg^{-1} i.p.	17	↔	33
	Indirect DA agonist	Amphetamine	0.5 and 1.0 mg kg^{-1} i.p.	17	↑	33
		D-Amphetamine	0.4–1.2 mg kg^{-1} s.c.	24	↑	34
		D-Amphetamine	0.25 and 0.5 mg kg^{-1} i.p.	8	↓(0.25 mg kg^{-1}) ↔(0.5 mg kg^{-1})	18
		D-Amphetamine	0.80 and 1.20 mg kg^{-1} i.p.	24	↑	35
		Cocaine	15 mg kg^{-1} i.p.	5	↑	36
Human						
	D2/3 antagonist	Haloperidol	1.5 mg p.o.	13	↔	19
	D2/3 agonist	Oramipexole	0.25 and 0.5 mg p.o.	10	↔	37
	Indirect DA agonist	D-Amphetamine	10 mg or 20 mg p.o.	36	↓(20 mg) ↔(10 mg)	17
		L-dopa	150 mg p.o.	13	↑	19
	Opioid					
Animal						
	Unspecific opioid receptor antagonist	Naloxone	0.3, 1.0 and 3.0 mg kg^{-1} i.p.	16	↔	27
		Naltrexone	0.01, 0.1, 1.0 and 10 mg kg^{-1} s.c.	15	↔	25
	Mu-opioid receptor agonist	Morphine	0.3, 1.0, and 1.8 mg kg^{-1} s.c.	15	↑	25
		Morphine	0.3, 1.0, 3.0 and 6.0 mg kg^{-1} i.p.	16	↑(6.0 mg kg^{-1})	27
Human						
	Unspecific opioid receptor antagonist	Naltrexone	50 mg p.o.	18	↔	38

Abbreviations: DA, dopamine; fMRI, functional magnetic resonance imaging; i.p., intraperitoneal injection, intra-NAC, intra nucleus accumbens microinjections; N, number of subjects; NA, noradrenaline; p.o., per oral administration; s.c., subcutaneous injection; TYR/PHE, tyrosine/phenylalanine. All studies are within-subject, unless marked 'B' (between subject). Effects are abbreviated as: ↓ = decrease, ↔ = no effect, ↑ = increase. As the present study focused on cue-induced responding and reward impulsivity in humans, only representative animal studies are listed. For a more exhaustive review please refer to Holmes *et al.*[13] and Bari and Robbins.[39]

Supplementary Material for Study 3

Supplementary methods

Pavlovian-instrumental transfer task

The Pavlovian-instrumental transfer (PIT) task probes the ability of Pavlovian stimuli to increase instrumental reward responding even in the absence of any rewards. Accordingly, it is used to investigate reward-related behaviors, such as eating, drinking and drug taking, which are triggered by cues associated with drug or non-drug rewards. Controlled by Cogent software, a Med Associates M&M dispenser [Model ENV-702, St. Albans, VT] delivered individual M&M chocolates into a small bowl easily accessible to participants (Figure S1). To prevent auditory conditioning to the sounds made by the dispenser, participants wore headphones emitting constant 72-dB white noise. Before and after the task, as well as at the end of the experiment, participants were asked to indicate their desire for chocolate on a visual analogue scale from 0 (not at all) to 100 (very much): "Please mark on the scale how much you would want to eat M&Ms right now".

The PIT task followed a standard design according to the protocol of Lovibond and Colagiuri (2013), with an instrumental conditioning phase, a Pavlovian conditioning phase, and a transfer-test phase. In the instrumental phase, participants were instructed to press the space bar on their keyboard to earn chocolates. They received the following instructions: "During the first part of the experiment, you can press the space bar to obtain chocolates. You will need to press the space bar multiple times to earn each chocolate. You can press the space bar as much or as little as you wish. When you receive chocolate, please eat it. You can start pressing the space bar as soon as these instructions disappear." We used a variable-ratio (VR) 10 schedule, where on average 10 button-presses of the space bar (range=5–15) were required before a chocolate was delivered. For the first three rewards, fixed ratio schedules 2, 4, and 6 were used to induce button-pressing in participants. During the delivery of every chocolate reward, the word "chocolate" appeared in the center of the screen for 1 second. Additionally, for every button-press, a small black square appeared in the center of the screen for 0.1 seconds. Any participant that had not obtained at least five rewards in the first 5 minutes of the task was informed that they might have to press the space bar more than once in order to earn chocolate. The instrumental-acquisition phase completed either when

participants had obtained 12 rewards or once 10 minutes had passed. As in the previous study (Lovibond and Colagiuri, 2013), any participant who did not earn 12 rewards did not meet the criterion for the following parts of the task and was excluded from further analysis. In total, two placebo subjects, six amisulpride subjects, and six naltrexone subjects did not meet the criterion of the instrumental phase and were therefore excluded from the PIT analysis.

In the second phase, the Pavlovian phase, participants were instructed that they would see images on the computer screen and told not to press the space bar. The following instructions were displayed: "During the next part of the experiment, you will see some colored images and you may or may not receive chocolate. Please do not press the space bar during this part of the experiment." We used a differential-conditioning procedure. A red and a blue stimulus (counterbalanced) acted as the two conditioned stimuli (CS): CS+ and CS-. Every CS was presented 6 times for 10 seconds. The CS+ was always paired with the delivery of a chocolate reward, while the CS- was always presented with no outcome. The intertrial interval ranged from 15 to 35 seconds and trials were randomized such that no more than two trials of the same CS type were presented in a row.

In the final phase, the transfer-test phase, participants were instructed that they could now press the space bar again: "During the next part of the experiment, you may press the space bar again." In this phase, testing was carried out under instrumental and Pavlovian extinction, i.e., without any rewards. During the initial 2 minutes, instrumental extinction took place. Extinction was extended for another 30 seconds for any participants that pressed the space bar during the final 30 seconds of the extinction period. Once participants had stopped responding for the entire final 30-second period or 10 minutes had passed, the transfer test began. During the transfer test, the CS+ and the CS- were presented for 10 seconds in random order, while button presses were recorded. The two CSs were then presented again in random order. The intertrial interval ranged from 90 to 110 seconds. After this phase, participants rated how often each of the two CSs was immediately followed by chocolate during the second phase of the experiment, using a scale from 0 (never) to 100 (always). The difference between the rating for the CS+ and the rating for the CS- served as an index of participants' awareness of the Pavlovian contingencies.

Supplementary Results

Mood

With respect to the exploratory correlation analysis, we found that while there were no significant correlations between mood and behavioral outcomes in the PIT task ($|r|<0.18$,$p>0.30$, $N_{placebo}=38$, $N_{amisulpride}=35$, $N_{naltrexone}=34$), the impact of mood on delay discounting differed between the three groups. There was no correlation in the placebo group ($r=0.18$, $p=.28$, $N=39$), however, the amisulpride group showed a positive correlation between mood and the proportion of immediate rewards chosen in the delay discounting task ($r=0.31$, $p<.05$, $N=40$), while the naltrexone group showed a negative correlation ($r=-0.36$, $p<.05$, $N=40$). The comparison of the strength of the correlations between the three conditions using Fisher's Test to compare the correlation coefficients was significant for comparisons involving naltrexone (placebo vs. amisulpride: $p=.54$; placebo vs. naltrexone: $p<.05$; amisulpride vs. naltrexone: $p<.01$).

Supplementary discussion

Relation between tasks

One interesting finding of our study is that cue-induced responding, assessed by PIT, and reward impulsivity, measured by the delay discounting task, did not correlate. Furthermore, mood differentially modulated performance in these two tasks; specifically, mood had no effect on performance in the PIT task, while it affected performance in the delay discounting task. This could suggest that the PIT and delay discounting tasks are not measuring the exact same process and this is noteworthy as it is commonly assumed that *incentive salience* (or *wanting*) measured through cue-induced responding in the PIT task can be equated to *decision value/utility* measured by reward impulsivity in the delay discounting task (Berridge and Aldridge, 2008; Monterosso et al., 2012).

However, to our knowledge, no study in humans has directly compared participants' behavior in these two tasks. Studies in humans have primarily used the Barratt Impulsiveness Scale (BIS-11) questionnaire to measure trait impulsivity and reported conflicting results. While Watson and colleagues (2014) failed to find a correlation between trait impulsivity and the PIT transfer effect, Garofalo and colleagues (2015) report that participants, who were sign trackers, i.e., participants who unlike goal trackers focus more on the conditioned stimulus than the reward, had stronger PIT transfer effects as well as higher levels of trait impulsivity. It is important to note, however, that impulsivity is not one unified construct. Instead it can be parsed into at least three components: (1) self-reported i.e., trait impulsivity (measured by BIS-11); (2) impulsive action (measured for example by the Stop Signal Task) and (3) impulsive choice (measured by delay discounting) (Broos et al., 2012). In line with this, one animal study investigating individual differences in cue-induced responding differentiated between impulsive action and impulsive choice, and found that sign trackers tend to show stronger cue-induced responding and impulsive action, but did not differ from goal trackers in impulsive choices in a delay discounting task (Lovic et al., 2011). Together, it may be that specifically impulsive choice differs from the *incentive salience*/*wanting* behavior measured by the PIT task and that *decision value/utility* is not directly influenced by the same processes that enhance cue responding. However, one should keep in mind that the absence of

a correlation does not in itself offer definitive proof of a dissociation between these two constructs, and it would be interesting to probe this further in future studies.

Supplementary figures

Figure S1. Timing of the behavioral tasks. After completing questionnaires, participants received 400 mg amisulpride, 50 mg naltrexone or placebo in a randomized and double-blind fashion. After 3h (+/-1.10 min, SEM), participants underwent instrumental & Pavlovian training, followed by the PIT transfer test phase and the delay discounting task. Mood was assessed after completion of all tasks. Red arrows indicate blood plasma collection.

Figure S2. Illustration of the set-up of the Pavlovian-instrumental transfer task. Depiction of a participant during the transfer-test phase. A Pavlovian stimulus appears on the monitor, while the participant is pressing the instrumental key. During the prior instrumental and Pavlovian phases, M&Ms were dispensed into the white bowl to the left of the computer screen.

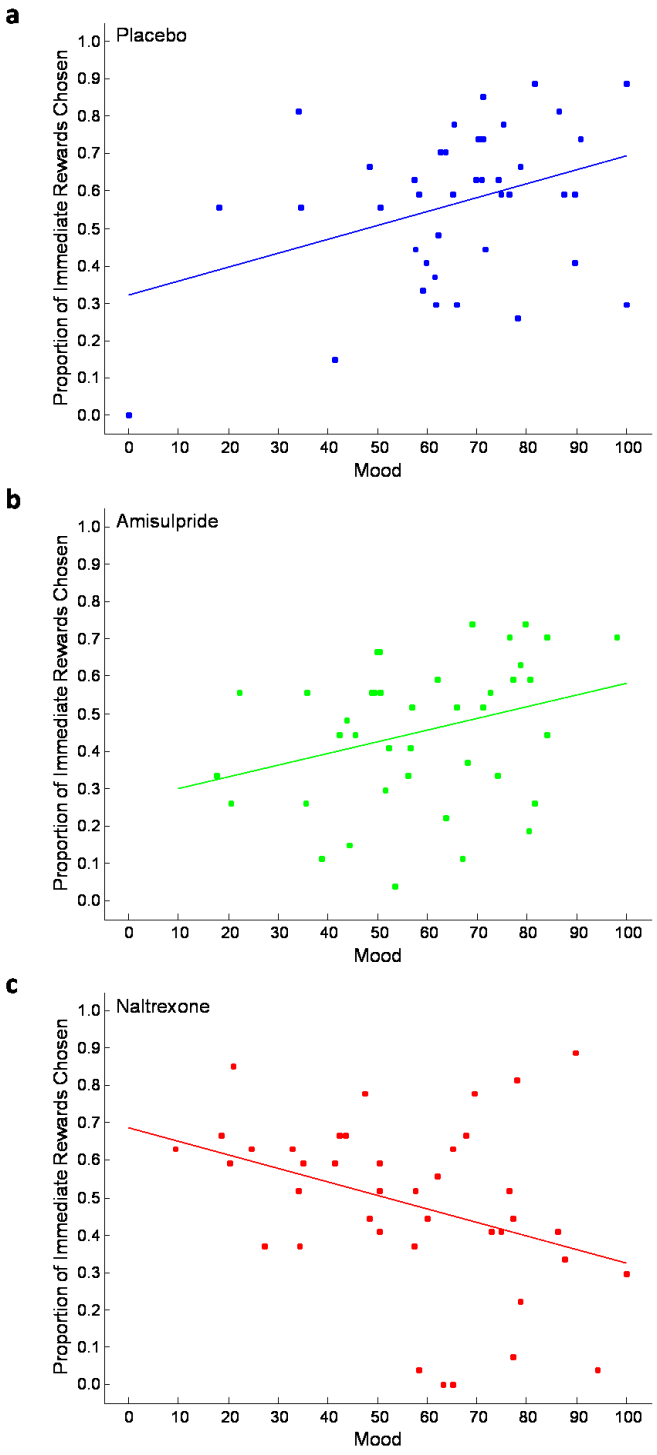

Figure S3. Correlations between mood ratings and the proportion of immediate rewards chosen in the delay discounting task. a-b The relationship of mood and discounting behavior was similar for participants in the **(a)** placebo and **(b)** amisulpride group, with mood and the number of immediate rewards chosen showing a positive relationship (placebo: r=.18, p=0.28, N=39; amisulpride: r=0.31, p<.05, N=40). **(c)** In contrast, for participants in the naltrexone group the relation was reversed, with positive mood being associated with higher propensity to choose delayed rewards (r=-0.36, p<.05, N=40).

Supplementary tables

Table S1. Final number of subjects used in each analysis.

	Placebo	Amisulpride	Naltrexone
	N	N	N
Demographic	40	41	40
PIT	38	35	34
DD	40	40	40
Mood	39	40	40
Mood correlation w/PIT	37	34	34
Mood correlation w/DD	39	40	40
Correlation between tasks	38	34	34

N number of subjects; *PIT* Pavlovian-instrumental transfer task; *DD* delay discounting task.
We excluded the following subjects: *PIT* → subjects who did not meet criterion; *DD* → one subject who had missing data; *Mood* → one placebo subject and one amisulpride subject with mood=zero (outlier); *Mood correlation PIT* → one subjects who did not meet criterion and subjects with mood=zero (outlier); *Mood correlation DD* → one amisulpride subject with missing data (and who had mood=zero) and one placebo subject with mood=zero (outlier); *Correlation tasks* → subjects who did not meet criterion for the PIT, one subject who had missing data in the DD.

Table S2. Performance of the placebo, amisulpride, and naltrexone groups during the Instrumental and Pavlovian phase, as well as the extinction period.

	Placebo (N=38)		Amisulpride (N=35)		Naltrexone (N=34)				
	Mean	SEM	Mean	SEM	Mean	SEM	F	df, df_{err}	p
Instrumental Phase									
Time until criterion (minutes)	2.73	0.47	2.25	0.31	2.41	0.34	0.41	2, 104	0.66
Number of Button-Presses	112.58	1.52	112.63	1.31	115.00	1.60	0.85	2, 104	0.43
Frequency of Button-Presses	1.37	0.14	1.30	0.14	1.30	0.14	0.08	2, 104	0.92
Pavlovian Phase									
Ratings of Contingencies	67.86	0.42	53.51	0.66	65.60	0.51	2.08	2, 104	0.13
Extinction Period									
Number of Button-Presses	9.19	1.08	10.53	1.06	9.39	1.08	0.45	2, 104	0.64

Table S3. Delay Discounting Results using Kirby's equation and logistic regression to estimate the discounting parameter k.

	Placebo (N=40)		Amisulpride (N=40)		Naltrexone (N=40)				
	Mean	SEM	Mean	SEM	Mean	SEM	F	df, df_{err}	p
Kirby's k	0.026	0.005	0.010	0.002	0.018	0.005	3.39	2, 117	0.04
Logistic k	0.026	0.006	0.011	0.002	0.020	0.005	2.91	2, 117	0.05

k indicates the discount rate parameter for which the value of the smaller immediate reward is equal to that of the larger delayed reward (indifference).

Table S4. Demographic data and questionnaire data of the placebo, amisulpride, and naltrexone groups.

	Placebo (N=40)		Amisulpride (N=41)		Naltrexone (N=40)				
	Mean	SEM	Mean	SEM	Mean	SEM	F	df, df_{err}	p
Age	22.15	0.38	21.46	0.38	21.65	0.33	0.96	2, 118	0.39
Body mass index	22.51	0.38	21.69	0.40	21.80	0.38	1.37	2, 118	0.26
Years of education	14.90	0.35	14.35	0.31	14.35	0.31	0.73	2, 118	0.48
Affect Intensity Measure[8]	3.33	0.05	3.36	0.06	3.45	0.87	0.92	2, 118	0.40
Action Regulating Emotion Systems[9]	54.09	1.02	55.15	0.92	54.80	1.05	0.29	2, 118	0.75
Behavioral Inhibition System (BIS)	21.81	1.03	22.71	0.77	22.58	0.95	0.27	2, 118	0.76
Behavioral Activation System (BAS)	32.28	0.42	32.44	0.41	32.23	0.48	0.07	2, 118	0.94
Barratt Impulsiveness Scale[10]	68.50	1.10	67.90	1.12	65.52	1.24	1.86	2, 118	0.16

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Curriculum Vitae

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